FORMULATION DESIGN, DEVELOPMENT AND EVALUATION OF EXTENDED RELEASE MATRIX TABLETS OF TRIMETAZIDINE HYDROCHLORIDE

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Submitted by

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DECLARATION BY THE CANDIDATE

I hereby declare that this thesis entitled **"FORMULATION DESIGN, DEVELOPMENT AND EVALUATION OF EXTENDED RELEASE MATRIX TABLETS OF TRIMETAZIDINE HYDROCHLORIDE"** is the result of original work carried out by me in **PGP College of Pharmaceutical Science and Research Institute,** under the guidance of **Mr.S.Suresh, Assistant Professor, Department of Pharmaceutics** for submission to Tamilnadu Dr. M.G.R Medical University,Chennai for the award of degree of **Master of Pharmacy** in **Pharmaceutics.** This work has not been submitted earlier in part or full to any other University or College for the award of any other degree.

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By

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1. INTRODUCTION[1]

Oral route of drug administration is oldest and safest mode of drug administration. It posses several advantages. It does not possess the sterility problem and minimal risk of damage at the site of administration. It provides accurate dosing without assistantship of administration. In conventional oral drug delivery system, there is little or no control over release of drug, and effective concentration at the target site can be achieved by administration of grossly excessive dosage form. This kind of dosing pattern result in constantly changing, unpredictable and often sub or supra therapeutic plasma concentration, leading to marked side effects in some cases. Moreover, the rate and extent of absorption from conventional formulation may vary greatly, depending on factor such as physiochemical properties of drug, presence of excipients, various physiological factors such as presence or absence of food, pH of gastrointestinal tract, G.I. motility etc.

The above problem can be minimized by oral controlled drug delivery. In oral controlled drug delivery the amount of drug release is constantly predetermined and these constant releases of drug provide a constant blood plasma level of drug for a therapeutic response. The oral controlled drug delivery have many advantage to conventional delivery- it decrease the fluctuation of drug plasma concentration, it reduce toxicity, provide a sustained effects, reduced the dosing frequency. Apart from other advantage it reduces total amount of drug used, improve patient compliance and reduced patient care time.

The disadvantage of oral controlled release product are longer time to achieve therapeutic blood concentration, possible increase variation in bioavailability after oral administration, enhanced first pass effect, dose dumping, sustained concentration in oral dose case, lack of doses flexibility and usually grater expense.

Hydrophilic polymers are widely used in oral controlled drug delivery due to their flexibility to produce desirable drug release profile, cost effectiveness, and broad regulatory acceptance. Among the hydrophilic polymers, HPMC (hydroxyproylmethylcellulose) is the most widely used carrier for the preparation of oral controlled drug delivery system due to its properties such as its ability to swell upon jellification once contact with water, and its very low toxicity and easy of manufacture, the gel becomes a viscous layer acting as a protective barrier to both influx of water and efflux of drug in the solution. On the other hand, hydrophobic polymer, such as EC can be alternative to the swelling polymers by forming an inert matrix with no physiological action and stable at different pH values and moisture levels when a tablet with hydrophobic matrix is placed in the dissolution medium, the drug at surface is released quickly, with a possible burst effects, requiring its replacement drug from inner layers that must diffuse through the pores until it reaches the surface.

Physician can achieve several desirable therapeutics advantages by prescribing sustained release dosage form. Since, the frequency of drug administration is reduced, patient's compliances can be improved and the drug administration can be made more convenient as well. The blood level oscillation characteristics of multiple dosing form of conventional dosage form is reduced, because more even blood level is maintained in the design of sustained release dosage form. The total amount of drug administered, thus maximum availability with a minimum dose. In addition, the safety margin of high potency drug can be increased and the incidence of both local and systemic adverse effects can be reduced in sensitive patients. Overall, increased administration of sustained release dosage form gives increased reliability.

Sustained release technology is relatively new field and as a consequence, research in the field has been extremely fertile and has produced many discoveries. With many drugs, the basic goal is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time.

The design of proper dosage form is an important element to accomplish this goal. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release and depot dosage form are term used to identify drug delivery system that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. In the case of oral sustained released dosage form, an effect is for several hours depending upon residence time of formulation in the GIT.

Not all the drugs are the suitable candidates for the sustained release dosage form. Ideal characteristic of the drug for the sustained release dosage form are;

- Drug should have a shorter half-life as drug with a longer half-life are inherently long acting drugs.

- Drug should be absorbed from large portion of gastrointestinal tract, since absorption must occur through the gut.

- Drug should be having a good solubility profile to be a good candidate for sustained release dosage form.

- Dose of the drug should not be too large, as a larger dose is to be incorporated into sustained release dosage form.

1.1 POTENTIAL ADVANTAGE OF SUSTAINED RELEASE DOSAGE FORM[2]:

1) Avoid patient's compliance problem due to reduced frequency of dosing.

2) Blood level oscillation characteristics of multiple dosing of conventional dosage form are reduced because a more even blood level is maintained.

3) Employ a less total drug.

4) Minimize or eliminate local or systemic side effects.

5) Minimize drug accumulation with chronic dosing.

6) Obtained less potential of reduction in drug activity with chronic use.

7) Improved efficiency in treatment.

8) Cure or control condition more promptly.

9) Improved control of condition i.e. reduced fluctuation in drug level.

10) Improved bioavailability of some drugs.

11) Make a use of special effects, e.g. sustained release aspect for relief of arthritis by dosing before bedtime.

12) Economy.

13) Overall, administrations of sustained release form enable increased reliability of therapy.

.

1.2 MATRIX SYSTEM[3,4]:

The matrix system is most often used for a drug-controlled release from a pharmaceutical dosage form. Among the innumerable method used in controlled release drug from pharmaceutical dosage form, the matrix system is the most frequently applied; it is release system for delay and control of the release of the drug that is dissolved or dispersed in a resistant supports to disintegration.

To define matrix, it is necessary to know the characters that differentiate it from other controlled release dosage forms. Hence the following must be considered:

- The chemical nature of support (generally, the support are formed by polymeric net)
- The physical state of drug (dispersed under molecular or particulate form or both).
- The matrix shape and alteration in volume as a function of time.
- The route of administration (oral administration remains the most widely used but other routes are adaptable).
- The release kinetic model.

1.3 THE CLASSIFICATION OF MATRIX SYSTEM:

Mineral matrix:

Drug retained in the support.

Drug adsorbed on the support

Lipidic matrix:

Delivery by diffusion.

Delivery by surface erosion

Hydrophillic matrix:

Unlimited swelling, delivery by diffusion.

Limited swelling controlled delivery through swelling

Inert matrix:

Controlled delivery by diffusion

Biodegradable matrix:

Non-Lipidic.

1.4 ADVANTAGES OF MATRIX SYSTEM

The interest awakened by matrix system in last few years is completely justified in view of the major advantages. Among these, the following stand out. With proper control of manufacturing process, reproducible release profiles are possible.

There is no risk of “dumping” of a large part of dose, through the structure makes the immediate release of a small amount of active principle unavoidable.

Their capacity to incorporate active principle is large, which suits them to delivery of large dosage

1.5 PRINCIPAL OF MODIFIED DRUG RELEASE [5,6]:

Following either of the two principles can modify drug release.

1.5.1 Barrier principal

In this method the retardant material is imposed between the drug and elusion medium. Drug release is by diffusion of the drug through the barrier and /or erosion of the barrier or permeation of the barrier by moisture

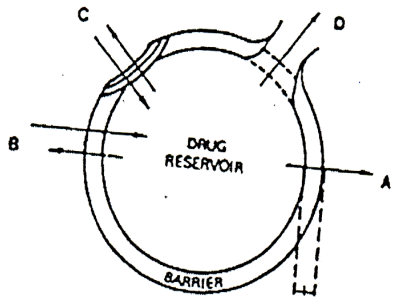

Figure no.1.

Barrier mediated models of sustained release dosage form regimen.

A. Drug diffusion through the barrier,

B. permeation of barrier by elution media followed by drug dissolution,

C. Erosion of barrier releasing drug,

D. rupture of permeation of elutiomedia.

1.5.2 Embedded matrix:

In this drug is dispersed/embedded in a matrix of retardant material that may be encapsulated in a particulate form or compressed into the tablet. Drug release occurs by permeation of water leaching extraction of diffusion of drug from the matrix and erosion of matrix material.

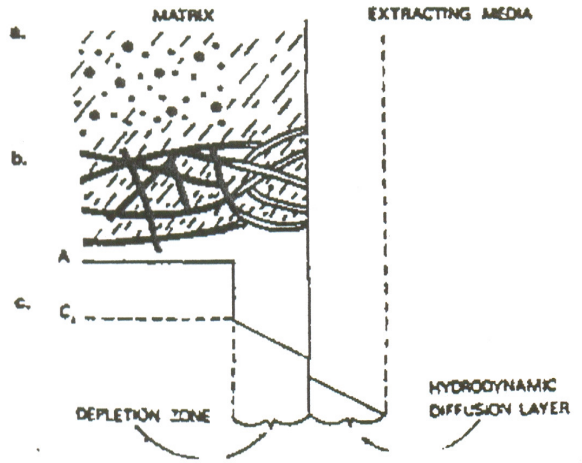

Figure No. 2

Embedded matrix concept as a mechanism of controlled released in sustained release

A. dosage form design network model a drug is insoluble in the retardant material.

B Drug is soluble in the retardant material. Diffusion profile etc. Characterize drug release from matrix system.

1.6 SWELLABLE MATRIXS AS SYSTEM FOR ORAL DELIVERY [7]:

Monolithic devices or matrices represent a substantial part of drug delivery systems. Matrices containing swellable polymers are referred to as

Hydrogel matrices
Swellable control release systems.
Hydrophillic matrix tablet

Swellable matrices for oral administration are commonly manufactured as tablet by compression of hydrophilic microparticulate polymers. Therefore, the most appropriate classification for these systems is swellable matrix tablet. They are constituted of a blend of drug and one or more hydrophilic polymers.

The release of drug from swellable matrix tablet is based on glassy-rubbery transition of polymer as a result of water penetration into the matrix. The interaction between water, polymer and drug are the primary factors for drug release. However, various formulation variables such as polymer grade, drug–polymer ratio, drug solubility and drug and polymer particle size, can influence drug release rate to greater or lesser degree.

The central element of the mechanism of drug release in the gel layer (rubbery polymer), which is formed around the matrix. The gel layer is capable of preventing matrix disintegration and further rapid water penetration.Water penetration, polymer swelling, drug dissolution and diffusion and matrix erosion are phenomenon determining gel layer thickness. Finally drug release is controlled by drug diffusion through the gel layer and/or by erosion of the gel layer.

1.7. MECHANISMS OF DRUG RELEASE FROM MATRIX SYSTEM [8,9]

The release of drug from controlled devices is via dissolution of the matrix or diffusion of drug through the matrix or a combination of the two mechanisms.

1.7.1. Dissolution controlled systems

A drug with slow dissolution rate will demonstrate sustaining properties, since the release of the drug will be limited by the rate of dissolution. In principle, it would seem possible to prepare extended release products by decreasing the dissolution rate of drugs that are highly water-soluble. This can be done by:

Preparing an appropriate salt or derivative

Coating the drug with a slowly dissolving material – encapsulation dissolution control Incorporating the drug into a tablet with a slowly dissolving carrier – matrix dissolution control (a major disadvantage is that the drug release rate continuously decreases with time).

The dissolution process can be considered diffusion-layer-controlled, where the rate of diffusion from the solid surface to the bulk solution through an unstirred liquid tablet is the rate-determining step. The dissolution process at steady-state is described by the Noyes-Whitney equation:

$$\mathbf{Dc/dt = kDA(Cs-C) = D/hA(Cs-C)}$$

dC	-	dissolution rate
kd	-	the dissolution rate constant (equivalent to the diffusion coefficient Divided by the thickness of the diffusion layer D/h)
D	-	Diffusion coefficient
Cs	-	saturation solubility of the solid
C	-	Concentration of solute in the bulk solution

Equation 1 predicts that the rate of release can be constant only if the following parameters are held constant: surface area, diffusion coefficient and diffusion layer thickness and concentration difference. However, under normal conditions, it is unlikely

that these parameters will remain constant, especially surface area, and this is the case for combination diffusion and dissolution systems.

1.7.2. Diffusion controlled systems

Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier, which is usually a water-insoluble polymer. In general, two types or subclasses of diffusion systems are recognized: reservoir devices and matrix devices.

1.7.2.1. Reservoir devices

In these formulations where tablet coating constitutes the main factor in controlling drug release. Examples of materials used to control drug release include hardened gelatin, methyl or ethyl cellulose, polyhydroxymethacrylate, methacrylate ester copolymers, and various waxes. Ethyl cellulose and methacrylate ester copolymers are the most commonly used systems in the pharmaceutical industry.

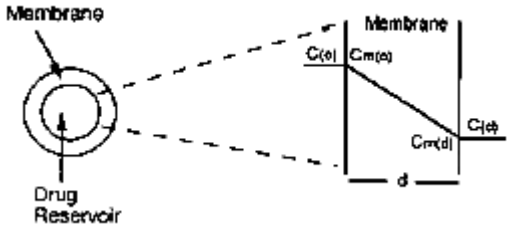

Figure3. Schematic representation of a matrix release system

1.7.3 Bioerodible and combination diffusion and dissolution system

Bioerodible devices constitute a group of system for which mathematical description of release kinetics can be quite complex. Bioerodible matrix system consists of the drug dispersed in an erodible matrix.

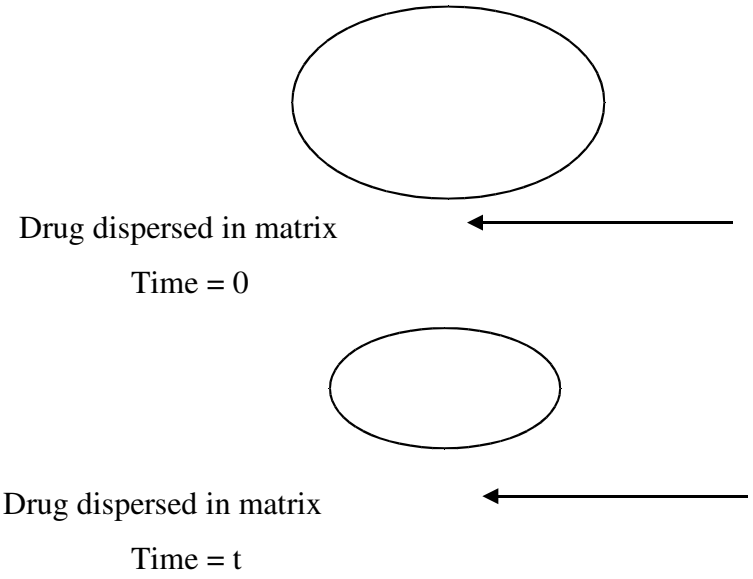

Figure 4: Representation of a Bioerodible matrix system.

Drug dispersed in the matrix before release at time = 0. At time = t release by drug diffusion or matrix erosion has occurred.

The mechanism of release from simple erodible slab, cylinders, and sphere has been described .by Eq. A simple expression describing release from all three of these erodible devices is

$$M1/M = 1- (1-K0t/C0a)n$$

Where n=3 for a sphere, n=2 for a cylinder and n=1 for a slab. The radius of a sphere, or cylinder, or the half-height of a slab is represented by a. Mt is the mass of a drug released at infinite time. As a further complication, these systems can combine diffusion and dissolution of both matrix material and the drug. Not only can drug diffuse out of the dosage form, but also the matrix itself undergoes a dissolution process. The

complexity of the system can arise from the fact that, as the polymer dissolves, the diffusional path-length for the drug changes. These usually result in a moving boundary diffusion system. Zero order release can occur only if surface erosion occurs and surface area dose not change with time. The inherent advantage of such a system is that bioerodible property of the matrix dose not result in a ghost matrix.

The disadvantages of these matrix systems are that release kinetics is often hard to control, since many factors affecting to both the drug and the polymer must be considered. Another method for the preparation of bioerodible system is to attach the drug directly to the polymer by a chemical bond. Generally, the drug is released from the polymer by hydrolysis or enzymatic reaction. This makes control of the rate of release somewhat easier. Another advantage of the system is the ability to achieve very high drug loading, since the amount of drug placed in the system is limited only by the available sites on the carrier.

A third type, which in this case utilizes a combination of dissolution and diffusion, is that of a swelling controlled matrix. In this the drug is dissolved in the polymer, instead of an insoluble or erodible polymer. This allows entrance of water which causes dissolution of drug and diffusion out of the swollen matrix.

In these systems the release rate is highly dependent on polymer-swelling rate, drug solubility, and the amount of soluble fraction in the matrix. This system usually minimizes burst effects, since polymer swelling must occur before drug release.

1.8 ADVANTAGES OF HYDROPHILIC MATRIX TABLET [10,11,12] :

1) With proper control of the manufacturing process, reproducible release profiles are possible. The variability associated with them is slightly less than that characterizing coated release form.
2) Structure allows an immediate release of small amount of active principle there is no risk of dose dumping.
3) Their capacity to incorporate active principle is large, which suits them to delivery of large doses.
4) The manufacturing processes are notably simple. Tablet formulation can be done via direct compression or by wet granulation techniques.
5) Large variety of nonexpensives gelling agents is approved for oral use by the Competent official organization.
6) The safety margin of high-potency drugs can be increased.
7) The drug release from hydrophilic matrices show a typical time dependent profile i.e. decreased drug release with time because of increased diffusion path length.

1.9 FACTORS INFLUENCING THE DRUG RELEASE FROM MATRIX:

- Choice of matrix material.
- Amount of drug incorporated in the matrix.
- Viscosity of the hydrophilic material in aqueous system at a fixed
- Concentration.
- Drug: matrix ratio.
- Tablet hardness, porosity, and density variation.
- Entrapped air in tablet.
- Tablet shape and size.
- Drug particle size.
- Solubility of drug in aqueous phase.
- Surfactants and other additives.

1.10 TABLET MANUFACTURING METHODS [13] :

Tablets are manufactured by wet granulation, Dry granulation or direct compression method.

1] Wet Granulation

Wet granulation is the process in which a liquid is added to a powder in a vessel equipped with any type of agitation that will produce agglomeration or granules. These granules after drying are compressed to form tablet.

2] Dry Granulation

In this technique, there is no use of liquids. The process involves the formation of slugs. Then the slugs are screened or milled to produce granules. The granules formed are then compressed to form tablet.

3) Direct compression

The term direct compression is used to define the process by which tablet is compressed directly from powder blends of active ingredient and suitable excipients, which will flow uniformly in the die cavity and forms a firm compact.

1.11 DRUG PROPERTIES RELEVENT TO CONTROLLED RELEASE FORMULATIONS

The design of controlled - release delivery systems is subject to several variables of considerable importance. Among these are the route of drug delivery, the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. Each of these variables are interrelated and this imposes certain constrains upon choices for the route of delivery, the design of the delivery system and the length of therapy. Properties of drugs are very important for designing a sustained release dosage form mainly physicochemical and biological properties of the drug are most important.

1.11.1 Physicochemical properties:

A) Aqueous solubility and pKa:

A drug to be absorbed it must be dissolved in the aqueous phase surrounding the site of administration and then partition into the absorbing membrane. Two of the most important physicochemical properties of a drug that influence its absorptive behavior are its aqueous solubility and if it is a weak acid or base its pKa. These properties pay an influential role in the performance of controlled release systems.

The aqueous solubility of a drug influences its dissolution rate, which in turn establishes its concentration solution and hence the driving force for diffusion across membrane.

Dissolution rate is related to aqueous solubility as shown by the Noyes-Whitney equation that, under sink condition is:-

$$dc/dt = KDACS$$

Where, dc/dt = Dissolution rate

KD = Dissolution rate constant.

A = Total surface area of the drug particles.

Cs = Aqueous saturation solubility of the drug.

The dissolution rate is constant only if surface area 'A' remain constant, but the important point to note is that the initial rate is directly proportional to aqueous solubility Cs. Therefore, aqueous solubility of a drug can be used as a first approximation of its dissolution rate. Drugs with low aqueous solubility have low dissolution rates and usually suffer oral bioavailability problems.

Aqueous solubility of weak acids and bases is governed by the pKa of the compound and pH of the medium.

For weak acid,

$$\mathbf{St = So\ (1+ka/[H+]) = So(1+10\ pH - pKa)\ldots\ldots\ldots\ldots...(1)}$$

Where,

St = Total solubility (both ionized and un-ionized forms) of the weak acid

So = Solubility of the un - ionized form

Ka = Acid Dissociation constant

H+ = hydrogen ion concentration of the medium. .

Equation (1) predicts that the total solubility, st of a weak acid with a given pKa can be affected by the pH of the medium.

For a weak base,

$$\mathbf{St = So\ (1+[H+]\ /\ Ka = So\ (1+10\ Pka - PH)\ \ldots\ldots\ldots\ldots\ldots\ (2)}$$

Where ,

St = Total solubility (both conjugate acid and free base forms) of the weak base.

So = Solubility of the free base form

Ka= Acid dissociation constant of the conjugate acid.

So total solubility, St of a weak base whose conjugate acid has a given pKa, which can be affected by the pH of the medium.

In general, extremes in the aqueous solubility of a drug are undesirable for formulation into controlled release product. A drug with very low solubility and a slow dissolution rate will exhibit dissolution limited absorption and yield an inherently sustained blood level.

Formulation of such a drug into a controlled release system may not provide considerable benefits over conventional dosage forms. Any system upon diffusion of drug through a polymer as the rate - limiting step in release would be unsuitable for a poorly soluble drug, since the driving force for diffusion is the concentration of drug in the polymer or solution, and this concentration would be low. For a drug with very high solubility and a rapid dissolution rate, it is often quite difficult to decrease its dissolution rate to slow its absorption. Preparing a slightly soluble form of a drug with normally high solubility is, however, one possible method for preparing controlled release dosage forms.

B) **Partition Coefficient**

Between time that a drug is administered and the time is eliminated from the body, it must diffuse through a variety of biological membranes that act primarily as lipid like barriers.

A major criteria in evaluation of the ability of a drug to penetrate these lipid membranes is its apparent oil / water partition coefficient defined as

$$K = C0/CW$$

Where,

Co = Equilibrium concentration of all forms of the drug e.g ionized and unionized in an organic phase at equilibrium.

Cw = Equilibrium concentration of all forms in aqueous phase.

In general, drugs with extremely large values of 'K' are very oil soluble and will partition into membrane quite readily. According to Haunch correlation, the logarithm of the activity of a drug or its ability to be absorbed and the logarithm of its partition coefficient having parabolic relationship. The explanation for this relationship is that the activity of a drug is a function of its ability to cross membranes and interact with the receptor. The more effectively a drug crosses membranes, the greater its activity. The

optimum partition coefficient value of a drug in which it most effectively permeates membranes and thus shows the greatest activity.

The value of K at which optimum activity is observed is approximately 1000/1. Drugs with a partition coefficient that is higher or lower than the optimum is, in general, poorer candidates for formulation into controlled-release dosage forms.

C) Drug stability

One important factor for oral dosage forms is the loss of drug through acid hydrolysis and/or metabolism in the GI tract. Since a drug in the solid state undergoes degradation a much slower rate than a drug in suspension or solution. It is possible to improve significantly the relative bioavailability of a drug that is unstable in the stomach; the most appropriate controlling unit would be one that releases its content only in the intestine. The reverse in the case for those drugs that are unstable in the environment of the intestine, the most appropriate controlling unit in this case would be one that releases its contents only in the stomach, so, drugs with significant stability problems in any particular area of the GI tract are less suitable for formulation into controlled release systems that deliver their content uniformity over the length of the GI tract. Controlled drug delivery systems may provide benefits for highly unstable drugs because the drug may be protected from enzymatic degradation by incorporation into a polymeric matrix.

D) **Protein Binding**

There are some drugs which having tendency to bind with plasma proteins (e.g. Albumin) and causes retention of the drug in the vascular space. The main force of attraction responsible for binding is vanderwal forces, hydrogen bonding and electrostatic forces. In general, charged compounds, because of electrostatic effects.

If a drug binds with protein then the distribution of the drug into the extravascular space is governed by the equilibrium process of dissociation of the drug from the protein. The drug-protein complex can serve therefore as a reservoir in the vascular space for controlled drug release to extravascular tissues, but only for those drugs that exhibit a

high degree of binding. Thus, the protein binding characteristics of a drug can play a significant role in its therapeutic effect, regardless of the type of dosage form.

Extensive binding to plasma proteins will be evidenced by a long half-life of elimination for the drug and such drugs generally does not required a controlled-release dosage form, however, drugs that exhibit a high degree of binding to plasma protein also might bind to biopolymers in the GI tract, which could have an influence on controlled-drug delivery.

E) Molecular size and diffusivity:

Drugs in many controlled-release systems must diffuse through a rate controlling membranes or matrix. The ability of a drug to diffuse through membranes, it's so called diffusivity [diffusion coefficient), is a function of its molecular size (or molecular weight). An important influence upon the value of the diffusivity. 'D', in polymers is the molecular size for molecular weight) of the diffusing species. For most polymers, it is possible to relate logD empirically to some function of molecular size as

$$\textbf{Log D = -Sv log V + Kv = - SM logM + Km}$$

Where,

V = molecular Volume.

M = molecular weight.

SV,Sm,Kv, Km = constant

The value of 'D' thus is related to the size and shape of the cavities as well as size and shape of drugs. Generally, values of the diffusion coefficient for intermediate molecular, weight drugs, i.e.150 to 400, through flexible polymers range from 10^{-6} to 10^{-9} cm2 / sec, with values on the order of 108 being most common. A value of approximately 10^{-6} is typical for these drugs through water as the medium. For drugs with a molecular weight greater than 500, the diffusion co-efficient in many polymers frequently are so small that they are difficult to quantify, i.e., less than 10-12 cm2/sec. Thus, high

molecular weight drugs and/or polymeric drugs should be expected to display very slow release kinetics in controlled release devices using diffusion through polymeric membranes or matrices as the releasing mechanism.

1.11.2. Formulation variables

The physicochemical characteristics of the drug, in particular its aqueous solubility, should be considered in the formulation of a matrix system. Other drug properties affecting system design include drug stability in the system and at the site of absorption, pH-dependent solubility, particle size and specific surface area.

Drug particle size

Effect of drug particle size on release is important in the case of moderately soluble drugs. In the case of water-soluble aminophylline or propranolol HPMC-based tablet an increase in drug particle size did not significantly alter the release rate of the drug. A noticeable effect was seen only at a low drug: HPMC ratio and at a large drug particle size (above 250µm), in this case, rapid dissolution of the water soluble drug would leave a matrix with low tortuosity and high porosity. Another study showed that for a given effective surface area, diclofenac particle size influenced the release rate from HPMC tablet. The smallest particle size of drug dissolved more easily when dissolution medium penetrated through the matrix resulting in a greater role for diffusion. The larger particle size dissolved less readily and therefore was more prone to erosion at the matrix surface.

Drug: polymer ratio

For diclofenac tablet formulated with HPMC, an increase in polymer: drug ratio reduced the release rate. This was because an increase in polymer concentration caused an increase in the viscosity of the gel (by making it more resistant to drug diffusion and erosion) as well as the formation of a gel layer with a longer diffusional path. Diffusional release of the water soluble drug metoprolol decreased with increasing HPMC incorporation. By varying the polymer level (Methocel® K4M 10-40%), Nellore et al. (1998) achieved different metoprolol in vitro release profiles.

Polymer type

Various grades of commercially available HPMC differ in the relative proportion of the hydroxypropyl and methoxyl substitutions; increasing the amount of hydrophilic hydroxypropyl groups leads to a faster hydration: Methocel® K >Methocel® E > Methocel® F. Generally rapid hydrating Methocel® K grade is preferred, especially for highly soluble drugs where a rapid rate of hydration is necessary. It is important to note that an inadequate polymer hydration rate may lead to dose dumping, due to quick penetration of gastric fluids into the tablet core (Dow Pharmaceutical Excipients, 1996). In each grade, for a fixed polymer level, the viscosity of the selected polymer affects the diffusional and mechanical characteristics of the matrix. By comparing different Methocel® K viscosity grades, the higher viscosity gel layers provided a more tortuous and resistant barrier to diffusion, which resulted in slower release of the drug (metoprolol HCl). Sung et al. (1996) compared different viscosity grades of HPMC (Methocel® K100LV, K4M, K15M, K100M). The fastest release of adinazolam mesilate was achieved for the K100LV formulation. The K4M formulation exhibited a slightly greater drug release than K15M and K100M. Due to the lack of a significant difference in the release profiles between K15M and K100M, the authors suggested a limiting HPMC viscosity of 15000cP, above which, if viscosity increased, the release rate would no longer decrease. In the case of ethyl cellulose, the findings are completely different. The lower viscosity grades of ethyl cellulose are more compressible than the higher viscosity grades, resulting in harder tablet and slower release.

Fillers

A study the effect of filler (57% of the tablet weight) on a metoprolol formulation at 20% Methocel® K4M level. They concluded that filler solubility had a limited effect on release rate. The release profiles showed a decrease of about 5-7% after 6h, as the filler was changed from lactose to lactose – microcrystalline cellulose then to dicalcium phosphate dihydrate -microcrystalline cellulose. Addition of soluble fillers enhanced the dissolution of soluble drugs by decreasing the tortuosity of the diffusion path of the drug, while insoluble fillers like dicalcium phosphate dihydrate got entrapped in the matrix. Also, it was assumed that the presence of swelling insoluble filler like microcrystalline

cellulose changed the release profile to a small extent due to a change in swelling at the tablet surface. Changing the filler from 100% dicalcium phosphate dihydrate to 100% lactose resulted in an increase in metoprolol release from Methocel® K100LV tablet at 4, 6 and 12h this was explained by dissolution of lactose and the consequent reduction in the tortuosity and or gel strength of the polymer. Similar dissolution profiles were obtained for filler concentration up to 48%. No dose dumping due to stress cracks (Dow Pharmaceutical Excipients, 1996) during gelling were observed in the case of insoluble fillers.

Polymeric excipients

A study reported that non-ionic polymers did not alter drug release significantly from HPMC matrices; however, ionic polymers were capable of retarding the release of oppositely charged molecules. They studied the effect of polymeric additives (non-ionic polyethylene glycol 6000 or ethyl cellulose, cationic diethylaminoethyl dextran, anionic sodium carboxymethyl cellulose Na-CMC) on drug release (chlorpheniramine maleate, sodium salicylate and potassiumfenoxymethylpenicillin) from HPMC matrix (85%). Non-ionic polymers (15% of tablet weight) did not significantly alter the release rates. Na-CMC (50% replacement of HPMC) reduced the chlorpheniramine maleate release in pH 7 buffer (near zero order release), but not in an acidic medium. There was a complexation of the drug with the anionic polymer; which was not possible below pH 3, when Na-CMC was in its unionized insoluble form. As a result of the complexation, the gel erosion became the prominent release mechanism instead of diffusion. No interaction occurred between sodium salicylate and Na-CMC (both anionic). In the presence of diethylaminoethyl dextran, sodium salicylate release was slower at pH 7, but not altered at pH 1 (when the drug was present in its unionized form). Overall, the effect of ionic polymers incorporated into HPMC matrices on the release of oppositely charged drugs was small. The drug-polymer ionic complexation approach in designing oral dosage formulation for controlled release of buspirone. Anionic exchange polymers sodium carboxymethyl cellulose and methacrylic acid /ethylacrylate copolymer were recommended based on the complexation affinity and dispersability in the aqueous environment of the gastrointestinal tract. The weight ratio of buspirone to anionic

exchange polymer varied between 4:1 and 1:6, preferably between 2:1 and 1:4. In addition to facilitating the controlled release of buspirone, the formulations increased the bioavailability and reduced the inter-individual variability. Therefore, the buspirone-ion exchange polymer HPMC tablet permitted enhanced targeting of therapeutic amounts and effects of the drug. The addition of anionic polymers (Eudragit® S, Eudragit® L 100-55, and Na-CMC) on the release of weakly basic propranolol hydrochloride from HPMC matrices. The interaction between propranolol hydrochloride and anionic polymers influenced the drug release. The HPMC: anionic polymer ratio also affected the drug release. The matrix containing HPMC: Eudragit® L 100-55 (1:1) produced pH-independent extended release tablet. An optimization procedure to determine the HPMC: e-carrageenan ratio (34:30) required for a pH-independent release of chlorpheniramine maleate. e-Carrageenan was added to overcome the increase in diffusion path length and decrease in the release rate associated with HPMC systems. e-carrageenan was subjected to erosion, which was higher at acidic pH.

1.11.3 PROCESS VARIABLES

A) Compression force:

The compression force had a significant effect on tablet hardness; its effect on drug release from HPMC tablet was minimal. It could be assumed that the variation in compression force should be closely related to a change in the porosity of the tablet. However, as the porosity of the hydrated matrix is independent of the initial porosity, the compression force seems to have little influence on drug release. The changes in compression force or crushing strength had minimal effect on drug release from HPMC matrix tablet once critical hardness was reached. Increased dissolution rates were observed when the tablets were found to be extremely soft, and this phenomenon was attributed to a lack of powder compaction, as tablet hardness was only 3 kp.

B) Tablet shape:

The size and shape of the tablet for the matrix system undergoing diffusion and erosion might impact the drug dissolution rate. Modification of the surface area for metoprolol tartrate tablet formulated with Methocel® K100LV from the standard

concave shape (0.568 sq. in.) to caplet shape (0.747 sq. in.) showed an approximately 20-30% increase in dissolution at each time point. Based upon these results, the researchers concluded that for maximum uniformity of extended release characteristics, tablet matrices should be manufactured to be as spherical as possible, in order to produce the minimum release rate, with regard to tablet shape. Varying the aspect ratio (radius/height) of the HPMC tablet is a very easy and effective tool to modify the release rate of the matrix system.

Release rate for tablet with the same volume was higher for flat shape (ratio = 20) than regular cylinders (ratio 2) and almost rod-shaped cylinders (ratio 0.2). The results were attributed to difference in tablet surface area. A mathematical model was proposed that could employ in order to calculate the optimal aspect ratio and size of a cylindrical tablet required to achieve a specific release profile. The model takes into account Fickian diffusion of water in and drug out of the tablet and swelling; it does not take into account dissolution and it cannot be applied for water insoluble drugs, which are released by dissolution process. The mathematical model proposed above was then used to predict the dissolution rates of propranolol hydrochloride and chlorpheniramine maleate (water soluble drugs).

C) Tablet size:

For tablet having the same aspect ratio and drug concentration, the tablet size had a very strong influence on the release rate; within 24 hours, 99.8% was released from the small tablet, 83.1% from the medium size and 50.9% from the large tablet. It was hypothesized that the smaller tablet released drug more rapidly due to an increased surface area per volume. Additionally, it was concluded that larger diffusion pathways existed in the larger tablet leading to a decrease in drug release.

1.11.4 BIOLOGICAL PROPERTIES

I) Absorption:

The rate, extent and uniformity of absorption of a drug are important factors when considering it's formulation into a controlled - release system. Since the rate limiting step in drug delivery from a controlled-release system is its release from a dosage form, rather than absorption, a rapid rate of absorption of drug relative to its release is essential if the 'system is to be successful. In case of controlled release dosage form Kr<<< Ka this becomes most critical in the case of oral administration. Assuming that the transit time of a drug through the absorption half-life should be to 4 hrs. This corresponds to a minimum absorption rate constant Ka of 0.17 to 0.23 hr necessary for about 80 to 95 % absorption over a 9 to 12 hr transit time. For a drug with a very rapid rate of absorption, (i.e. Ka >>0.23 hr-1), the above discussion implies that a first order release rate constant Kr < 0.17 hr-1 is likely to result in unacceptable poor bioavailability in many patients. Therefore, slowly absorbed drugs will be difficult to formulate into controlled release systems where the criteria that Kr <<< Ka must be met.

II) Distribution:

The distribution of a drug into vascular and extravascular spaces in the body is an important factor in its overall elimination kinetics. Two parameters that are used to describe the distribution characteristics of a drug are its apparent volume of distribution and the ratio of drug concentration in the tissue is that in plasma at the steady state called T/P ratio. The magnitude of the apparent volume of distribution can be used as a guide for additional studies and as a predictor for a drug dosing regimen and hence there is a need to employ a controlled-system.

III) Metabolism:

Drugs that are significantly metabolized before absorption, either in the lumen or: tissue of the intestine can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, less total drug is presented to the enzymatic process during a

specific period allowing more complete conversion of drug to its metabolite. Formulation of these enzymatically susceptible compounds as prodrug is another viable solution.

IV) Biological Half Life:

The usual goal of an oral sustained release product is to maintain therapeutic blood levels over an extended period. To this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life. Each drug has its own characteristics elimination rate, which is the sum of all elimination processes including metabolism, urinary excretion and all other processes that permanently remove drug from blood stream. Therapeutic compounds with short half-life are excellent candidates for sustained-release preparations, since this can reduce dosage frequency. However, this is limited, in that drugs with very short biological half life as it may require excessively large amounts of drug in each dosage unit to maintain sustained effect, forcing the dosage form itself to become limitingly large.

In general, drugs with half-life shorter than two hrs are poor candidates for sustained release preparations. Drugs with long half-life, more than 8 hrs, are also generally does not be used in sustaining forms, since their effect is already sustained.

V) Side Effects and Safety Considerations:

There are very few drugs whose specific therapeutic concentrations are known. Instead, a therapeutic concentration range is listed, with increasing toxic effects expected above this range and a fall off in desired therapeutic response observed below the range.

The most widely used measure of the margin of safety of a drug is its therapeutic index, (Tl).

$$\mathbf{TI = LD50/ ED50}$$

Where,

LD50 = median lethal dose

ED50 = median effective dose

For very potent drugs, whose therapeutic concentration range is narrow, the value TI is small. In general, larger the value of TI, Usually are poor candidates for formulation into controlled-release product. A drug is considered to be relatively safe if its TI value exceeds 10.

VI) Dose Size:

Since a controlled-release system is designed to alleviate repetitive dosing, it is naturally contain greater amount of drug that a corresponding conventional dosage form. For lose drugs requiring large conventional doses, the volume of sustained dose may be so large so to be impractical or unacceptable, depending on the route of administration. The same may be true for drugs that require a large release rate from the controlled-release system, e.g., drugs with shorter half-life. For oral route, the volume of the product is limited by patient acceptance.

AIM AND OBJECTIVE

The aim of this study is to formulate and evaluate the extended release tablets of **Trimetazidine hydrochloride**.

2.1 REASONS FOR USING TRIMETAZIDINE HYDROCHLORIDE IN EXTENDED RELEASE FORMULATION:-

- **Trimetazidine hydrochloride** is prescribed to Patients to prevent the pain of chest due to lack of oxygen to the muscles of heart.
- **Trimetazidine hydrochloride** in the Extended release is used to improve the bioavailablity
- **Trimetazidine hydrochloride** in the Extended release is used to improve the Patients non compliance.

2.2 REASONS FOR SELECTION OF DOSAGE FORM

- The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to promptly achieve and maintain the defined drug concentration.
- In pharmaceutical practice, drug administration to patient exists in several approaches, one of which is conventional, i.e. drug is given several times a day, to produce desired therapeutic effect.
- Due to frequent dosing, fluctuation in the drug blood level occurs; hence maintenance of defined drug level can be above or below the minimum therapeutic level. The conventional tablet provides only a single transient release of drug.
- Hence the above potential problem can be minimized or reduced by formulating the drug in release control matrix i.e. sustain release system .This system minimizes or eliminates side effects, provide patient compliance, economically and promptly achieves and maintains the desired effect.

Hence due to above properties, it may be more efficient to deliver the drug at a sustained manner, at a reduced input rate compared with oral

conventional dose occurring from a Extended release dosage form **Trimetazidine hydrochloride** is available in market, presently.

2.3 The main objective of present study:-

- The present study is to investigate the possibility of developing extended release dosage form for the drug **Trimetazidine hydrochloride** by using polymers HPMCK15CR & Ethyl cellulose and Metalose in different ratios as matrix
- It can be achieved by planning for trails until the desired release pattern is obtained. The aim is to evaluate the release profile of drug from fabricated extended release tablets.

3. PLAN OF WORK

I. **Literature survey**

II. **Preformulation studies -**

- Drug excipients compatibility study by IR spectra
- Determnation of λ max
- Bulk density
- Tapped density
- Carr's Index (Compressibility Index)
- Hausner's Ratio

III. Preparation of Matrix tablets by using matrix forming polymers

- Method
  - By Wet granulation method

IV. Evaluation of Matrix tablets by

- Thickness
- Hardness
- Weight variation
- Friability
- In-vitro drug release study
- Swelling Index

V. Stability study.

4. REVIEW OF LITERATURE

Review of literature showed that the matrix formulation for oral administration of many drugs are tried using various polymers and other release retardants

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P. D. NAKHAT *et.al.*[14] "Developing sustained release matrix tablets of diclofenac sodium by using different drug: polymer ratios. Xanthan gum w as used as matrix former, and microcrystalline cellulose as diluent. All the lubricated formulations were compressed using 8 mm flat faced punches. Hence, Xanthan gum can be used as an effective matrix former, to extend the release of diclofenac sodium".

Chowdary KPR *et al.*[15] "Olibanum and its resin and carbohydrate fractions were evaluated as rate controlling matrix materials in tablets for controlled release of diclofenac. Diclofenac matrix tablets were formulated employing olibanum and its resin and carbohydrate fractions in different concentrations and the tablets were evaluated for various tablet characters including drug release kinetics and mechanism. Diclofenac matrix tablets formulated employing olibanum and its resin component provided slow and controlled release of diclofenac over more than 24 h. Drug release from the matrix tablets was by Fickian diffusion and followed first order kinetics".

S C Basak *et al.*[16] "Monolithic matrix tablets of ambroxol hydrochloride were formulated as sustained release tablets employing hydroxypropyl methylcellulose polymer, and the sustained release behaviour of the fabricated tablets was investigated. Sustained release matrix tablets containing 75 mg ambroxol hydrochloride were developed using different drug polymer ratios of hydroxypropyl methylcellulose".

J.P.G. Brakenhoff *et al.* [17] "The effect of age and renal function on the pharmacokinetic profile of a modified release tablet of trimetazidine (TMZ MR 35 mg) administered twice daily.

Methods- Study 1: Twelve healthy elderly subjects (CL_{creat} 72±8 ml/min, 72±4 years mean±SD) and eight young volunteers (CL_{creat} 134±18 ml/min, 25±8 years) received TMZ MR 35 mg b.i.d. (eight doses). Study 2: eight patients with severe renal failure ($CL_{creat.}$ 17±5 ml/min, 54±10 years), five patients with moderate renal failure ($CL_{creat.}$ 39±6 ml/min, 54±15 years) and eight volunteers ($CL_{creat.}$ 104±17 ml/min, 53±9 years) received TMZ MR 35 mg b.i.d. (patients: ten doses, volunteers: eight doses). Serial blood and urine samples were obtained following administration of the last dose in each study. TMZ plasma and urine concentrations were determined by gas chromatography (NPD-detector). The resulting data were analysed using standard non-compartmental pharmacokinetic methods".

Basak SC *et al.* [18] "Monolithic matrix tablets of ambroxol hydrochloride were formulated as sustained release tablets employing hydroxypropyl methylcellulose polymer, and the sustained release behaviour of the fabricated tablets was investigated. The results of dissolution studies indicated that a decrease in release kinetics of the drug was observed on increasing polymer ratio. The mechanism of drug release from the optimized formulation was diffusion coupled with erosion (anomalous)".

R.K.Khar *et al.* [19] "Compressed tablets were prepared from theophylline and guar gum. Effect of the viscosity grade of the polymer and polymer content in the tablets on release pattern of theophylline was examined in vitro. Release rate was retarded with increase in polymer content as well as the viscosity grade of polymer".

M. Marzilli *et al*[20]. "The efficacy of trimetazidine as an antianginal drug has been assessed in randomized, placebo-controlled studies, both as 'solo' treatment and in combination with betablockers and calcium channel blockers.In patients with chronic angina, trimetazidine increases work capacity and delays the appearance of symptoms and ECG changes during exercise. The benefits observed after acute administration are maintained in chronic treatment with trimetazidine, which is well tolerated by patients".

Balasubramaniam *et al*[21]. "Matrix tablets of cisapride and atenolol were prepared with varying proportions of hydroxypropylmethylcellulose of different viscosity grades viz; E15,E4M, K4M, And K15M, alone and combinations by wet granulation technique. The study also indicated that the amount of drug released decreased with an increase the polymer concentration. The combination of the different viscosity grades did not provide any additional advantage".

P D Nakhat *et al.*[22] "In the present investigation, an attempt has been made to increase therapeutic efficacy, reduce frequency of administration, and improve patient compliance, by developing sustained release matrix tablets of diclofenac sodium. Sustained release matrix tablets of diclofenac sodium, were developed by using different drug: polymer ratios, such as F1 (1:0.12), F2 (1:0.16), F3 (1:0.20), F4 (1:0.24) and F5 (1:0.28). Xanthan gum was used as matrix former, and microcrystalline cellulose as diluent. All the lubricated formulations were compressed using 8 mm flat faced punches".

Haider S.S. *et al.*[23] " Sustained release preparetations of metoclopramide HCl were prepared using carnauba wax and stearic acid as matrix formers. Granules were prepared by melt dispersion method while tablets were made by direct compression".

The fastest release rate was observed at pH 4.5 and the slowest at pH 1.2 which coincides with the drug's solubility behavior. The drug release kinetics followed the Higuchi's square root model in all cases

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Rathnanand M. ***et al.***[24] studied to develop sustained release matrix tablets of Terbutaline Sulphate.The tablets were prepared by wet granulation method using isopropyl alcohol with stearyl alcohol as granulating agent. Hydrophilic matrix materials like hydroxypropylmethylcellulose(HPMC), hydrophobic polymer such as Eudragit RLPO where used in the study. All the formulations exhibited Higuchi-dominated drug release. The mechanism of drug release was found to be diffusion controlled.

Thapa P. ***et al.***[25] studied the effect of different viscosity grade of HPMC and drug solubility on in-vitro release from matrix tablets. In addition to release mechanism, the release rate and mean dissolution time for propranolol HCl, salicylic acid and furosemide was compared using Krosmeyer-peppas equation. The release mechanism was found to be predominately diffusion controlled, anomalous, and case II transport type.

Nashiru Billa ***et al.***[26] studied processing variables at the laboratory and pilot scales that can affect hydration rates of xanthan gum matrices containing diclofenac sodium and the rate of drug release. Drug release was linear from xanthan gum matrices prepared at the laboratory scale and pilot scales; however, release was faster from the pilot scales.

M. Helena Amaral *et al.*[27] "effect of the concentration of hydrophilic (hydroxyl propyl methyl cellulose [HPMC] and hydrophobic (hydrogenated castor oil [HCO] products, fillers (lactose and dibasic calcium phosphate), and buffers (sodium bicarbonate, calcium carbonate, and sodium citrate) on naproxen release rate was studied.

Robert O. Williams III *et al.*[28] studied a reverse-phase high-performance liquid chromatographic (HPLC) method for recovery of the lipophilic drug, alprazolam, from matrix tablets containing the hydrophilic polymer hydroxylpropylmethylcellulose (HPMC) was developed. The recovery method reported here in was shown to be the most efficient to achieve complete recovery of alprazolam from powder blends and tablets containing a variety of excipients and different grades of HPMC.

Sandip B. Tiwari *et al.*[29] studied the effect of concentration of hydrophilic (hydroxypropyl methylcellulose [HPMC]) and hydrophobic polymers (hydrogenated castor oil [HCO], ethylcellulose) on the release rate of tramadol were studied. Hydrophilic matrix tablets were prepared by wet granulation technique, while hydrophobic (wax) matrix tablets were prepared by melt granulation technique. Hydro-phobic matrix tablets resulted in sustained in vitro drug release (>20 hours) as compared with hydrophilic ma-trix tablets (<14 hours). The presence of ethylcellulose in either of the matrix systems prolonged the release rate of the drug.

K. Raghuram Reddy *et al.*[30] studied to develop once-daily sustained-release matrix tablets of nicorandil, a novel potassium channel opener used in cardiovascular diseases. The tablets were prepared by the wet granulation method. Ethanolic solutions of ethylcellulose (EC), Eudragit RL-100, Eudragit RS-100, and polyvinylpyrrolidone were used as granulating agents along with hydrophilic matrix materials like hydroxypropyl methylcellulose (HPMC), sodium carboxymethylcellulose, and sodium alginate. The results of dissolution stud-ies indicated that formulation (drug-to-HPMC, 1:4; ethanol as granulating agent) could extend the drug release up to 24 hours.

Svetlana Ibric *et al.*[31] studied to model the effects of the concentration of Eudragit L 100 and compression pressure as the most important process and formulation variables on the in vitro release pro-file of aspirin from matrix tablets formulated with Eudragit L 100 as matrix substance and to optimize the formulation by artificial neural network.

Srisagul Sungthongjeen *et al.*[32] "Effect of 2 formula-tion variables, the pectin type (with different degrees of es-terification [DEs] and the amount of calcium, on drug re-lease from pectin-based matrix tablets. The results were more pronounced in phosphate buffer, where the phosphate ions induced the pre-cipitation of calcium phosphate. In conclusion, both pectin type and added calcium affect the drug release from the pec-tin-based matrix tablets".

Meena Rani *et al.*[33] studied to Prepared and comparative evaluation of fabricated matrix (FM), osmotic matrix (OM), and osmotic pump (OP) tablets for controlled delivery of diclofenac sodium (DS). It was concluded that the osmotic matrix and osmotic pump tablets could provide more prolonged, controlled, and gastrointestinal environmental independent DS release that may result in an improved therapeutic efficacy and patient compliance.

Saleh M. Al-Saidan *et al.*[34] "Develop guar gum matrix tablets for oral controlled release of water-soluble diltiazem hydrochloride. Matrix tablets of diltiazem hydrochloride, using various viscosity grades of guar gum in 2 proportions, were prepared by wet granulation method and subjected to in vitro drug release studies. Based on the results of in vitro and in vivo studies it was concluded that that guar gum matrix tablets provided oral controlled release of water-soluble diltiazem hydrochloride".

Mohammad Reza Siahi *et al.*[35] "Design oral controlled delivery systems for the water-soluble drug, verapamil hydrochloride, using natural and semisynthetic polymers as carriers in the forms of 1- and 3-layer matrix tablets. Verapamil hydrochloride 1-layer matrix tablets containing hydroxylpropylmethylcellulose, tragacanth, and acacia either alone or mixed were prepared by direct compression technique.

The results also showed that the location of the polymers in the 3-layer tablets has a pronounced effect on the drug release. Kinetic analysis of drug release from matrices exhibiting sustained release indicated that release was predominantly attributable to the contribution made by Fickian diffusion, while the erosion/relaxation mechanisms had a minor role in the release".

Bhupinder Singh *et al.*[36] Design oral controlled release mucoadhesive compressed hydrophilic matrices of atenolol and to optimize the drug release profile and bioadhesion using response surface methodology. A central composite design for 2 factors at 3 levels each was employed to systematically optimize drug release profile and bioadhesive strength. Carbopol 934P and sodium carboxy methyl cellulose were taken as the independent variables. Besides unraveling the effect of the 2 factors on the various response variables, the study helped in finding the optimum formulation with excellent bioadhesive strength and controlled release.

Jaleh Varshosaz *et al.*[37] developed matrix sustained release tablets of highly water-soluble tramadol HCl using natural gums (xanthan [X gum] and guar [G gum]) as costeffective, nontoxic, easily available, and suitable hydrophilic matrix systems compared with the extensively investigated hydrophilic matrices (ie, hydroxypropyl methylcellulose [HPMC]/carboxymethyl cellulose [CMC] with respect to in vitro drug release rate) and hydration rate of the polymers. Tablets with only X had the highest mean dissolution time

(MDT), the least dissolution efficiency (DE8%), and released the drug following a zero-order model via swelling, diffusion, and erosion mechanisms. Guar gum alone could not efficiently control the drug release, while X and all combinations of natural gums with HPMC could retard tramadol HCl release. However, according to the similarity factor (f2), pure HPMC and H8G2 were the most similar formulations to Topalgic-LP as the reference standard.

Carla Martins Lopes *et al.*[38] was studied to produce a quick/slow biphasic delivery system for ibuprofen. A dual component tablet made of a sustained release tableted core and an immediate release tableted coat was prepared by direct compression. Both the core and the coat contained a model drug (ibuprofen). The sustained release effect was achieved with a polymer (hydroxyl propyl methylcellulose [HPMC] or ethyl cellulose) to modulate the release of the drug. The in vitro drug release profile from these tablets showed the desired biphasic release behavior: the ibuprofen contained in the fast releasing component was dissolved within 2 minutes, whereas the drug in the core tablet was released at different times (≈16 or 924 hours), depending on the composition of the matrix tablet. Based on the release kinetic parameters calculated, it can be concluded that the HPMC core was suitable for providing a constant and controlled release (zero order) for a long period of time.

Amelia Avachat *et al.*[39] Develop and characterize an oral controlled release drug delivery system for concomitant administration of diclofenac sodium (DS) and chondroitin sulfate (CS). A hydrophilic matrix-based tablet using different concentrations of hydroxyl propyl methylcellulose (HPMC) was developed using wet granulation technique to contain 100 mg of DS and 400 mg of CS. In conclusion, the in vitro release profile and the mathematical models indicate that release of CS and DS can be effectively controlled from a single tablet using HPMC matrix system.

Hamdy Abdelkader *et al.*[40] was investigating different types and levels of hydrophilic matrixing agents, including methylcellulose (MC), sodium alginate (Alg), and sodium carboxy methylcellulose (CMC), in an attempt to formulate controlled-release matrix tablets containing 25 mg baclofen. The tablets were prepared by wet granulation. Prior to compression, the prepared granules were evaluated for flow and compression characteristics. In vitro, newly formulated controlled-release tablets were compared with standard commercial tablets (Lioresal and baclofen). The prepared matrix tablets showed good mechanical properties (hardness and friability). MC- and Alg-based tablet formulations showed high release-retarding efficiency, and good reproducibility and stability of the drug release profiles when stored for 6 months in ambient room conditions, suggesting that MC and Alg are good candidates for preparing modified release baclofen tablet formulations

Atul Kuksal *et al.*[41] was studied to prepare and characterize extended-release matrix tablets of zidovudine using hydrophilic Eudragit RLPO and RSPO alone or their combination with hydrophobic ethyl cellulose. Release kinetics was evaluated by using United States Pharmacopeia (USP)-22 type I dissolution apparatus. The in-vitro drug release study revealed that either Eudragit preparation was able to sustain the drug release only for 6 hours (94.3% ± 4.5% release). Combining Eudragit with ethyl cellulose sustained the drug release for 12 hours (88.1% ± 4.1% release). Fitting the in vitro drug release data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release. In vivo investigation in rabbits showed sustained-release pharmacokinetic profile of zidovudine from the matrix tablets formulated using combination of Eudragits and ethylcellulose. In conclusion, the results suggest that the developed sustained-release tablets of zidovudine could perform therapeutically better than conventional dosage forms, leading to improve efficacy and better patient compliance.

Punna R. R. *et al.*[42] ,Oral controlled release matrix tablets of zidovudine were prepared using different proportions and different viscosity grades of hydroxypropyl methylcellulose. The effect of various formulation factors like polymer proportion, polymer viscosity and compression force on the in vitro release of drug were studied. In vitro release

studies revealed that the release rate decreased with increase in polymer proportion and viscosity grade. Mathematical analysis of the release kinetics indicated that the nature of drug release from the matrix tablets followed non-Fickian or anomalous release. The developed controlled release matrix tablets of zidovudine, with good initial release (17—25% in first hour) and which extend the release upto 16—20 h, can overcome the disadvantages of conventional tablets of zidovudine.

Nokheldchi A. ***et al.***[43], The effects of various polymers on the release of Diclofenac Sodium from matrics. In vitro release profile of Diclofenac Sodium from ethyl cellulose and HPMC K4M matrices showed that decreasing the concentration of Ethyl Cellulose and increase in the concentration of HPMC K4M resulted in an increase in the release rate of Diclofenac Sodium.

B.S. Nath ***et.al.***[44],The using a combined hydrophobic and hydrophilic matrix on the release of Theophylline. Combination of aliphatic alcohol (cetyl alcohol (cetyl alcohol) partially hydrated Methylcellulose was investigated as a sustain release matrix. The in-vitro release data showed that the total matrix component gave extended release of Theophylline for more than 8 hours and the drug release from the matrix indicated that the drug was released by diffusion obeying first order rate kinetics.

Chowdary K.P.R. ***et al.***[45] , Sustained release of Nifedipine tablets by using soliddispersion in HPMC with HPC and reported that its gave slow, controlled and complete release spread over a period of 12 hours. Drug release from these tablets followed zero order kinetics and release was by diffusion controlled.

M. Helena Amaral ***et al.***[46] , The effect of the concentration of hydrophilic (hydroxypropyl methylcellulose [HPMC]) and hydrophobic (hydrogenated castor oil [HCO])

products, fillers (lactose and dibasic calcium phosphate), and buffers (sodium bicarbonate, calcium carbonate, and sodium citrate) on naproxen release rate was studied. Matrix tablets were prepared by double compression, and In vitro dissolution tests were performed. The dissolution results showed that an increased amount of HPMC or hydrogenated castor oil resulted in reduced drug release.

Efentakis M., *et al.*[47] ,The effect of excipients on swelling and drug release from compressed matrices. The result showed that mechanisms are affected by the composition of matrix.

Efentakis. *et al.*[48] ,The influence of surfactant on drug release from a hydrophobic matrix. Hydrophobic materials were prepared using Eudragit R.L-100 and Flurbiprofen as a model drug and studied to determine the mechanism by which surfactant increase the rate of drug release. It was concluded that for the matrix the major mechanism by which surfactant increase drug dissolution rates is through the formation of pores to aid the access of dissolution fluid and egress of the dissolved drug.

Rippe EG, *et al.*[49] , A stabilized sustained release oral solid dosage form which includes an effective amount of tramodol or pharmaceutically acceptable salt therfof dispersed in matrix of a hydrophobic material comparising a wax-like substance which was melted or softened during the preparation of the matrix,is cured at a temperature from about 35 ^{0} C to 65 ^{0} C for a time period from about 4 to about 72 hour , such that the formulation.

Skoug J.W. *et al.* [50] ,The quantities evaluation of the mechanism of release of matrix sustained release dosage forms by measurement of polymer release.

Hsieh *et al.*[51] ,Reported a more elegant version of this device which utilized an inward releasing hemisphere. This hemisphere was coated with an impermeable membrane

barrier everywhere except a small aperture in the center of this circular face. Such a device has been applied to polypeptide hormone insulin.

Kawasheina I. *et al.*[52] ,A modified spherical agglomeration technique as an alternative to spray congealing method. The method of preparation will influence the releasing characteristics obtained.

Chinam Niranjan Patra *et al.*[53] ,Develop a bilayer tablet of propranolol hydrochloride using superdisintegrant sodium starch glycolate for the fast release layer and water immiscible polymers such as ethylcellulose, Eudragit RLPO and Eudragit RSPO for the sustaining layer. The formulations gave an initial burst effect to provide the loading dose of the drug followed by sustained release for 12 h from the sustaining layer of matrix embedded tablets. In vitro dissolution kinetics followed the Higuchi model via a non-Fickian diffusion controlled release mechanism after the initial burst release

Teerawat Sahasathian *et al.*[54] , The Sustained release systems in the forms of chitosan (CTS) tablet and extrude for releasing amoxicillin. The result showed that chitosan with the particle size less than 75 μm yielded the best controlled release pattern. Moreover, the tablets containing chitosan with particle size less than 75 μm were able to provide a significantly improved sustained release profile of amoxicillin compared to the release profile of a commercial capsule.

S. Prasanna *et. al.*[55], "To develop "once daily" sustained release tablets of aceclofenac by direct compression using hydroxypropyl methylcellulose-K4M (HPMC). The solubility studies of aceclofenac were conducted to select suitable dissolution media. The tablets were subjected to physicochemical, in vitro drug release and stability studies".

It was observed from the reviewer of literature that very less work has been done on the formulation of matrix devices of Zidovudine. So, it was proposed to take Zidovudine in the present study of formulation of matrix tablet. Further it was proposed to use Xanthan, Ethyl cellulose, Hydroxy propyl methyl cellulose (E.Lv-15), Carboxy Methyl cellulose Sodium and Eudragit L155 as polymer is very less work has been done on above polymers.

5.1 DRUG PROFILE[56-61]

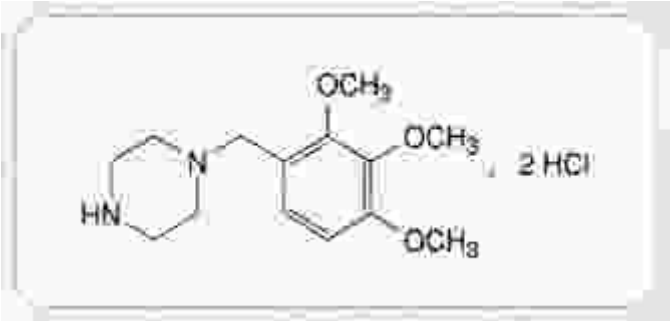

Figure No.5:- Structure of Trimetazidine HCL

Drug Name **:** Trimetazidine HCL

Chemical Name: 1-(2, 3, 4-Trimethoxybenzyl) piperazine hydrochloride. (TMZ).

Molecular Formula: $(C_{14}H_{22}N_2O_3)$ 2HCL

Molecular Weight **:** 339.26 g/mol.

Category: Antianginal (vasodilator) Trimetazidine (Di HCl) is used in angina and in ischaemia of neuro-sensorial tissues. To prevent the pain of chest due to lack of oxygen to the muscles of heart.

Solubility: very soluble in water, sparingly soluble in ethanol and practically insoluble in ether.

Melting Point: 227°C.

PHARMACOKINETICS:

PHARMACOKINETIC DATA:

- Bioavailability- 90%
- Protein binding –16%
- Metabolism - hepatic
- Half life – 6.0 +/- 1.4 hours
- Excretion - urinary
- Peak plasma concentration – 84 ng/ml
- T max – 1.8+/- .7 hrs
- Duration of action – 4 hrs or longer
- Volume of distribution is found to be 4.8 l/kg and plasma protien binding is 16 %.

PHARMACOLOGY:

Trimetazidine, known for years to be an effective antianginal agent, shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. By decreasing fatty acid oxidation, trimetazidine stimulates glucose utilization, restoring coupling between glycolysis and carbohydrate oxidation and leading to adenosine triphosphate production with lesser oxygen consumption. The antianginal properties of this agent are devoid of haemodynamic changes, and dramatically improve recovery of mechanical function after ischemia.

MECHANISM OF ACTION:

It has recently been demonstrated that, by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase, trimetazidine alters energy metabolism via inhibitory effects on fatty acid oxidation, thus favouring glucose oxidation. On the basis of this recent observation, trimetazidine is regarded as the prototype of a new class of antianginal agents: the 3-ketoacyl coenzyme A thiolase inhibitors. The benefits of increased glycolytic substrate utilization are attributed to a number of mechanisms. The number of moles of adenosine triphosphatase (ATP) produced per mole of carbon oxidized is approximately 29% higher for free fatty acids relative to glucose, but the number of moles of ATP produced per mole of oxygen consumed is 12% higher for glucose than for free fatty acid oxidation. Thus, in normal conditions, it is more efficient for the myocardium to utilize free fatty acids, but

during ischaemia glucose is a better substrate. By decreasing fatty acid oxidation and stimulating glucose utilization, trimetazidine restores coupling between glycolysis and carbohydrate oxidation, and leads to ATP production with less oxygen consumption. By stimulating membrane phospholipid turnover during ischaemia and reperfusion, trimetazidine redirects fatty acids toward phospholipids.

SIDE EFFECTS:

Trimetazidine hydrochloride is safe & well tolerated. In addition, the toxic dose being very high, the safety margin of this drug is wide. The most commonly encountered side effects are gastric discomfort, nausea, headache and vertigo.

INTERACTIONS:

No drug interactions so far have been reported .in particular no interactions have been reported with beta-blockers, calcium antagonists, nitrates, heparin, hypolipidemic agents or digitalis praparations.

5.2 POLYMER PROFILE [62,63]

1. HYDROXY PROPYL METHYL CELLULOSE K15CR (HPMC K100M)[62]

Non-Proprietary Names:

BP : Hypromellose

Ph Eur : Methyl hydroxy propyl cellulosum

USP : Hydroxy propyl methyl cellulose

Synonyms:

Cellulose, hydroxypropyl methyl ether, culminal MHPC; E-464, HPMC; Methocel; methyl cellulose propylene glycol ether, methyl hydroxypropylcellulose, Metolose, Pharmacoat.

Chemical Name: Cellulose, 2-hydroxypropyl methyl ether.

Empirical Formula & Molecular Weight :

According to European Pharmacopoeia:

It is a partly O-methylated & O-(2-hydroxypropylated) cellulose.

Available in several grades with different viscosity and extent of substitution. Grades may be distinguished by appending a no. indicative of the apparent viscosity, in mpas, of a 2% w/w aqueous solution at 20^0C.

According to USP XXII:

It specifies the substitution type by appending a 4-digit number to a non-proprietary name, e.g. HPMC1828. First 2 digits refers approximate % of methoxy group ($-OCH_3$) & last 2 digits refers approximate % of hydroxy propoxy group ($-OCH_2CHOHCH_3$) calculated on dried basis. Molecular weight is 10,000-1, 50,000 gm/mol.

Functional Category:

Coating agent, film former, stabilizing agent, suspending agent, tablet binder, viscosity – increasing agent.

Application in Pharmaceutical Formulation / Technology:

- Widely used in oral & topical pharmaceutical formulation.
- In oral product, HPMC is generally used as tablet binder, in film coating & as an extended release matrix tablets 2-5% w/w concentration is suitable as binder in either wet or dry granulation process.
- High viscosity grades may be used to retard the release of water-soluble drug from matrix at levels of 10-80%w/w in tablets and capsule.
- Depending on viscosity grade concentration between 2-10% w/w used as film forming solution to film-coat tablets. Lower viscosity grades are used in aqueous film coating solution while higher viscosity grades used with organic solvents.
- Also used as suspending and thickening agent in topical formulation, mainly in ophthalmic preparation, as it forms a clear solution with fewer undispersed fibers as compared to methylcellulose. So 0.45 –1% w/w used as thickening agent to vehicles for eye-drops or artificial tear solution.
- Also used as emulsifier, suspending agent & stability agent in topical gels & ointments. As a protective colloid it can also prevent droplets & particles to coalescing or agglomerating, thus inhibits sediment formation.
- Also used as adhesive in plastic bandage & wetting agent in topical gels & Ointments. As a protective colloid it can also prevent droplets and particles to coalescing or

agglomerating, thus inhibits sediment formation. Also used as adhesive in plastic bandage & wetting agent for hard contact lenses. Widely used in cosmetics & food products.

Description: Odorless & tasteless, white or creamy-white colored fibrous or granular powder.

Solubility:

In cold water forms viscous colloidal solution, practically insoluble in chloroform ($CHCl_3$), ethanol (95%) & water, but soluble in mixture of ethanol & dichloromethane.

Incompatibility:

It is incompatible with some oxidizing agent. As at is nonionic it can't complex with metallic salts and ionic organics to form insoluble points.

Stability & Stability Condition:

It is a stable material but hygroscopic after drying. Solutions are stable between pH 3-11. Increase in temperature decreases viscosity of solution, as it undergoes a reversible sol to gel transformation upon heating and cooling respectively and get point is 50-90^{0}C. Aqueous solutions are enzyme resistant, provide good viscosity during long-term storage, but aqueous solution liable to microbial contamination and should be preserved with an antimicrobial preservative. Stored in a well-closed container, in cool & dry place.

2. ETHYL CELLULOSE[63]

Nonproprietary Name:

BP : Ethyl Cellulose

Ph Eur : Ethyl Cellulosum

USP NF : Ethyl Cellulose.

Synonyms: Aquacoat ; E462 ; Ethocel ; Surelease.

Chemical Name: Cellulose ethyl ether.

Empirical Formula & Molecular Weight: Ethyl Cellulose with complete ethoxyl substitution (DS=3) is $C_{12}H_{23}O_6$ $(C_{12}H_{22}O_5)_n$ $C_{12}H_{23}O_5$, where "n" can vary to provide a wide variety of molecular weights.

Functional Category: Coating agent, flavoring agent, viscosity-increasing agent, tablet binder, tablet filler.

Application in Pharmaceutical Formulations:

- Used as a hydrophobic coating agent for tablets & granules. Ethyl cellulose coatings are used to modify the release of a drug, to mask unpleasant taste & to improve stability.
- Used as a matrix former to produce modified release tablets.
- High viscosity grades are used in drug micro-encapsulation.
- Used as a SR tablet coating material in a concentration of 2-3%.
- Used as thickening agent in topical formulations.

Description: It is a tasteless, free flowing, white to light tan-colored powder.

Solubility: Practically insoluble in glycerin, propylene glycol & water. Ethylcellulose that contains less than 46.5% ethoxyl group is freely soluble in chloroform, methyl acetate & tetrahydrofuran, in mixtures of aromatic hydrocarbon with ethanol (95%). Ethylcellulose that contains not less than 46.5% ethoxyl group is freely soluble in chloroform,ethanol (95%), ethyl acetate, methanol & toluene

Viscosity: Viscosity increases with an increase in the ethyl cellulose concentration.

Incompatibilities: Incompatible with paraffin wax & microcrystalline wax.

Stability & Storage Conditions: It shows oxidative degradation in presence of sunlight or UV light at elevated temperatures, which can be prevented by the use of anti-oxidants & additives that can absorb light at 230-340nm range. It should be stored at a temp. not exceeding 32°C (90°F). It shouldn't be stored next to peroxides of other oxidizing agents.

3. METALOSE[63]

Non-Proprietary Name:

USP: Hypermellose

Substitution Type: 2208

Viscosity Type : 100 mPa s

Chemical Name: Cellulose ethyl ether.

Functional Category: Viscosity-increasing agents, tablet binder, tablet Polymer.

Application in Pharmaceutical Formulations:

- Used as a hydrophobic coating agent for tablets & granules. Ethyl cellulose coatings are used to modify the release of a drug, to mask unpleasant taste & to improve stability.
- Used as a matrix former to produce modified release tablets.
- High viscosity grades are used in drug micro-encapsulation.
- Used as a SR tablet coating material in a concentration of 3-5%.
- Used as thickening agent in topical formulations.

Description: It is a tasteless, free flowing, white to Slightly Off-White Powder.

Viscosity: Viscosity type 100 mPa s.

Spesifications:

Ph : 5 - 8

Viscosity: 80 - 120

Loss on drying: 5.0 max

Hydroxpropoxy Content: 8.0 - 12.0

Stability & Storage Conditions: Storage Conditions: Store containers sealed and in dry place. Keep away from heat or sunlight.

5.3 EXCIPIENTS PROFILE[64]

1. STARCH[64]

Non-Proprietary Name:

BP : Maize starch, Potato starch, Wheat starch, Rice starch, Tapioca starch.

Ph Eur : Maydis amylum, Solani amylum, Tritici amylum, Oryzae amylum.

USP NF : Corn starch, Potato starch, Wheat starch.

Synonyms: Amido, amidon, amilo, amylum.

Chemical Name: Starch.

Empirical Formula: $C_6H_{10}O_5$.

Molecular Weight: 50,000-160,000.

Functional Category: Glidant and disintegrant; tablet and capsule; tablet binder.

Application in Pharmaceutical Formulation / Technology:

It is used as an excipient primarily in oral solid-dosage formulations as a binder, diluent, and disintegrant. In tablet formulations, freshly prepared starch paste is used at concentration of 5-25% w/w as a binder. Commonly used tablet disintegrants at concentrations of 3-15%.

Description: It occurs as an odorless and tasteless, fine white-colored powder comprising very small spherical or ovoid granules whose size and shape are characteristic for each botanical variety.

Moisture Content: 18%for potato starch

Swelling temperature: 64^0C

Solubility: Practically insoluble in cold ethanol (95%) and in cold water.

Stability and Storage Condition: Stable and stored in air tight container in a cool and dry place.

2. MAGNESIUM STEARATE[64]

Non-Proprietary Name:

BP : Magnesium Stearate

Ph Eur : Magnesii Stearas

USP NF : Magnesium stearate

Synonyms: E572, Hy Qual, Magnesium octadecanoate, stearic acid magnesium salts.

Chemical Name: Octadecanoic acid magnesium salt

Empirical Formula: $C_{36}H_{70}mg\ O_4$

Molecular Weight: 591.27

Structural Formula: $[CH_3\ (CH_2)_{16}\ COO]_2Mg$

Functional Category: It is used as tablet and capsule lubricant.

Application in Pharmaceutical Formulation / Technology:

- Used in Cosmetics, foods and pharmaceutical formulations.
- Primarily used in capsules and tablets manufacturing at a concentration in between 0.25% to 5.0%.

Description:

It is a fine, white, precipitated or milled, impalpable, greasy powder of low bulk density, having a faint, characteristics odor and taste. It readily adheres to the skin.

Moisture: Content: <4%

Solubility: Practically insoluble in ethanol (95%), ether and water. Slightly soluble in warm benzene and warn ethanol (95%)

Stability and Storage Condition: Stable and stored in well closed container in a cool and dry place.

3. MICROCRYSTALLINE CELLULOSE[64]

Synonym: Cellulose gel; crystalline cellulose; Avicel PH 101,102

Empirical Formula: $(C_6H_{10}O_5)_n$.

Molecular weight: Approx. 36000

Description: Purified, partially depolymerised cellulose occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. Available in different particle size grades with different properties, i.e., 101 and 102.

Density, bulk: 0.28 gm/cm3.

Density, tapped: 0.43 gm/cm3.

Solubility: Insoluble in water, dilute acids and most organic solvents. slightly soluble in sodium hydroxide solution.

Stability & Storage conditions: Stable, hygroscopic,Store in a well-closed container.

Incompatibilities: None cited in the literature.

Handling precautions: No restrictions.

Uses: Tablet binder/diluent(5-20%), tablet disintegrant(5-15%), tablet glidant(5-15%), anti-adherent(5-20%), capsule diluents (10-30%).

4. TALC[64]

It is hydrous magnesium silicate may contain a small amount of aluminum silicate and iron.

Nonproprietary Name: Purified Talc (BP); Talc (JP); Talc (USP).

Synonym: Atalc; hydrous magnesium calcium silicate; hydrous magnesium silicate; magnesium hydrogen silicate; powdered talc.

Empirical Formula:

$Mg_6 (Si_2O_5)_4 (OH)_4$

Description: A very fine, white to grayish-white, impalpable, odorless, crystalline powder. Adheres readily to skin, soft to touch and free from grittiness.

Typical Properties:

Density, bulk: 19-24 gm/cm^3.

Density, tapped: 48-62.5 gm/cm^3.

Acidity/Alkalinity: pH= 7-10 for a 20% w/v aqueous dispersion.

Solubility:Insoluble in water, organic solvents, cold acids and dilute alkalis.

Stability & Storage conditions: Talc is a stable material and may be sterilized by heating at 160^0 C for not less than 1 hour. Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities: Incompatible with quaternary ammonium compounds.

Handling Precautions: Observe normal precautions appropriate to the circumstances and the quantity of the material handled. Talc is irritant if inhaled and prolonged excessive exposure may cause pneumoconiosis. Eye protection, gloves, and a respirator are recommended.

Table no. 1:-Application in pharmaceutical formulation or technology:

Use	Concentration (%)
Dusting powder	(90-99%).
Glidant or tablets lubricant	(1-10%)
Diluents for tablets and capsules	(5-30%)

5. LACTOSE[64]:

It occurs in three forms: -monohydrate, α-anhydrous, α-anhydrous. Commercial lactose is mainly the β-monohydrate.

Chemical name: 4 – 0 - α-D galactopyranosyl-β-D- glucopyranose.4-(α-D-galactoside)-D-glucose.

Empirical Formula:	**Molecular Weight:**
$C_{12}H_{22}O_{11}$ (anhydrous)	342.30
$C_{12}H_{22}O_{11}H_2O$ (monohydrate)	360.31

Density (bulk):0.62gm/cm^3

Density (tapped):0.94gm/cm^3

Description: White to off white or creamy white crystalline particles or powder, odorless; sweet-tasting.

Solubility: It is practically insoluble in chloroform, ethanol and ether .soluble in 1in 4.63parts of water

Stability and Storage: Store in a well-closed container to prevent absorption of moisture and of odors. Under humid conditions mold growth may occur. Lactose may develop brown coloration on storage. This reaction is accelerated by warm-damp conditions.

Incompatibilities: A mallard type condensation is likely to occur between lactose and compounds with a primary amino group to form brown colored products. This reaction occurs more rapidly with amorphous then crystalline lactose.

Handling precautions: Gloves mask and eye protections are recommended.

Uses: It is used as filler, diluents in pharmaceutical preparation.

6. COLLOIDAL SILICON DIOXIDE[64]

Synonyme: Aerosil; cab-o-sil ; colloidal silica ; fumed silica ; silica anhydride.

Nonproprietary Name: Colloidal anhydrous silica (BP), silica colloidal is androecia (Ph Eur), colloidal silicon anhydrous (USP)

Empirical Formula: SiO2.

Molecular Weight: 60.08.

Density (bulk): 0.029-0.042g/cm^3.

Density (tapped):0.05g/cm^3.

Acidity/Alkalinity: pH= 3.5-4.4 (4% aqueous dispersion)

Solubility: Practically insoluble in organic solvent, water and acids; soluble in hot solution of alkali hydroxide. It forms a colloidal dispersion in water.

Description: It is submicroscopic fumed silica with a particle size of 15nm. It is light, loose, bluish white colored, odorless, tasteless powder. Several grades of colloidal silicon dioxides are commercially available.

Functional Category: Adsorbent; anticacking Agent; emulsion stabilizer, glident; suspending agents; disintegrants; thermal stabilizers; viscosity increasing agents.

Application in Pharmaceutical Formulation or Technology:

Use		**Concentration (%)**
Aerosols	:	0.5-2.0
Emulsion stabilizer	:	1.0-5.0
Glidants	:	0.1-0.5
Suspending and thickening agents	:	2.0-10.0

Stability and Storage Conditions: Aerosil is hygroscopic but adsorb large quantity of water without liquefying. Viscosity-increasing property is depends on pH.Aerosil powder should be stored in a well-closed container.

Incompatibilities: Incompatible with diethylstilbestrol preparations.

METHODOLOGY

Table No 2: Materials Used

S.No	Materials Used	Monograph	Sources
1.	Trimetazidine HCL	BP	Sharon Bio-Medicine LTD.
2.	Ethyl Cellulose	USP	Feicheng Rutai Fine Chemicals CO.Ltd.
3.	Metalose	I.P.	Arihant trading Co.Ltd.
4.	Hydroxy propyl methyl cellulose K-15CR	I.P.	Shineltsu LTD Japan.
5.	Lactose	I.P.	Berje, Chemical, Mumbai
6.	M.C.C.	I.P.	Relience cellulose Pvt. Ltd.
7.	P.V.P.K.30	I.P.	Jyoti Associated Indore
8.	Magnesium stearate	I.P.	Loba Chemie Pvt.Ltd.
9.	Talc	I.P.	J.B. Chemical.
10.	Pregelatinised Starch	I.P.	Loba Chemie Pvt.Ltd.
11.	HCL	-------	Laboratory.
12.	Isoprpyl alcohol	-------	Laboratory.

Table No 3: Instruments Used

S.No	Types	Manufactured by

1.	Digital Weighing Balance	Ohaus Corp. Pine Brook, NJ, USA.
2.	Hot air oven	Unilab, India.
3	Sieve No; # 12, 16,20, 60,100.	Shreeji, Pharmaceutical, Scientific & Laboratory Instruments., India.
4.	Compression Machine	CIP Machineries Pvt. Ltd., Ahmedabad, India.
5.	Roche Friabilator	Indian Equipment Corporation, Bombay.
6.	Monsanto Hardness Tester	Rupa Industries, India.
7.	Dissolution Test Apparatus	Electrolab, Model-TDT-08L, USP.
8.	U.V-Spectrophotometer	Shimadzu Corporation, Japan.
9.	Fourier Transform Infra Red Spectroscopy (FTIR)	Nexus-870, Thermo Nicolet, Manisha lab.
10.	Distillation Apparatus	Borosil, India.
11.	Water Bath	Unilab, India.
12.	Sonicator	Spincotech Pvt.Ltd., Italy.
13.	pH-meter	Elico Ltd. Hyderabad, India.

6.1 Identification of drug (Trimetazidine HCL) sample:

It was confirmed by

- Melting point
- FT-IR spectral analysis
- UV absorption maxima

6.1.1. Melting point determination

Melting point is the temperature at which the pure liquid and solid exist in equilibrium. In practice, it is taken as equilibrium mixture at an external pressure of 1 atmosphere; this is sometimes known as normal melting points. The Thiel's tube method of melting point determination in liquid paraffin was used in the present study. Melting point was found to be in the range of 227^0C which was in compliance with the official value.

6.1.2. FTIR Spectra:

IR spectra of drug in KBr pellets at moderate scanning speed between 4000-400 cm^{-1} was carried out using FTIR (Jasco FTIR 6100 type A). The peak values (Wave number) and the possibility of functional group shown in spectra which compare with standard value. The comparison of these results with Trimetazidine HCL chemical structure shows that the sample was pure Trimetazidine HCL.(Figure No.7).

6.1.3. UV absorption maxima of Trimetazidine HCL:

UV scanning was done for 10 mcg/ml drug solution from 200-400 nm in phoushphate buffer 6.8 as a blank using double beams UV/VIS spectrophotometer. The wavelength maximum was found to be at 269 nm (Figure No.11).

6.2. Characterization of Drug:

6.2.1 Physical description of Trimetazidine HCL: -

Organoleptic properties:

Trimetazidine HCL is White or almost white crystalline powder, odorless, slightly hygroscopic.

Solubility: very soluble in water, sparingly soluble in ethanol and practically insoluble in ether.

Melting point: Its melting point found to be 227°C.

6.3 Drug Excipients Compatibility study:

Compatibility of the drug with recipients was determined by FT-IR spectral analysis, this study was carried out to detect any changes on chemical constitution of the drug after combined it with the excipients. The samples were taken for FT-IR study.

6.4 Preparation of buffers:

6.4.1 Preparation of acidic buffers:-

- **Preparation of 0.2 M hydrochloric acid:**
  HCL diluted with water to contain 7.292 gm of HCl in 1000ml.
- **Preparation of 0.2 M sodium hydroxide solution-**
  Dissolve 8.0 g of sodium hydroxide pallets in 1000 ml of distilled water.

6.4.2 Preparation of phosphate buffer:

- **Preparation of 0.2 M potassium dihydrogen phosphate solution-**
  Dissolve 27.213 g of potassium dihydrogen phosphate in 1000 ml of distilled water to get 0.2 M potassium dihydrogen phosphate.

- **Preparation of 0.2 M sodium hydroxide solution-**
  Dissolve 8.0 g of sodium hydroxide pallets in 1000 ml of distilled water.

- **Preparation of phosphate buffer pH 6.8 -**
  Place 50 ml of 0.2 M potassium dihydrogen phosphate and add 5.6 ml of 0.2 M of sodium hydroxide. Dilute with distilled water to make up the volume up to 200ml.

6.5 Preperation of Standard Calibration curve of Trimetazidine HCL-

Weigh accurately 100mg of Trimetazidine Hcl WS into a 100-ml volumetric flask;Dissolve dilute to volume with phoushphate buffer pH.6.8 From the stock solution 10 ml was further diluted to 100 ml with purified water. Then from this solution aliquots of 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 1.4, 1.6, 1.8 and 2 ml were pipette out and made up to 10ml with phoushphate buffer pH 6.8 The Absorbance of above solution was measured at 269 nm by U.V.Spectrophotometer.

The spectrum peak point graph of absorbance of Trimetazidine HCL versus wave length was shown in Figure No.12.

6.6 Evaluation of Powder and Grannuals:

6.6.1 Angle of repose

Flowability of different batch of granules was determined by calculating angle of repose by fixed height method. A funnel with 10 mm inner diameter of stem was fixed at a height of 2 cm. over the platform. About 10 gm of sample was slowly passed along the wall of the funnel till the tip of the pile formed and touches the steam of the funnel. A rough circle was drawn around the pile base and the radius of the powder cone was measured.

Angle of repose was calculated from the average radius using the following formula.

$$\theta = \tan^{-} (h/r)$$

Where, θ = Angle of repose, h = Height of the pile, r = Average radius of the powder cone.

6.6.2. Bulk density and Tapped density

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) was measured then the graduated cylinder was closed with lid, set into the density determination apparatus (bulk density apparatus, electro lab, Mumbai). The density apparatus was set for 500 taps and after that, the volume (V_f) was measured and continued operation till the two consecutive readings were equal. The bulk density, and tapped density were calculated using the following formulas.

Bulk density $= W/V_o$

Tapped density $= W/V_f$

Where, V_o = initial volume

V_f = final volume.

6.6.3 Compressibility index:

The Compressibility index and Hausner ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index and the Hausner Ratio.

The compressibility index and Hausner ratio may be calculated using measured values for bulk density (ρ_{bulk}) and tapped density (ρ_{tapped}) as follows:

$$\text{Compressibilty Index} = \frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}} \times 100$$

6.6.4 Hausner Ratio:

It provides an indication of the degree of densification which could result from vibration of the feed hopper.

$$\text{Hausner Ratio} = \frac{\text{Tapped Density}}{\text{Bulk density}}$$

Lower Hausner ratio – Better flowability,

Higher Hausner ratio – Poor flowability

6.7 Formulation of Trimetazidine HCL Matrix Tablets:

Each quantity mentioned will be taken in mgs,

Total weight of the tablet = 180mg

Each tablet contains = 35mg of the Trimetazidine HCL

Table No.4: Formulation of Trimetazidine HCL Matrix Tablets

Ingrdients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Trimetazidine Hcl	35	35	35	35	35	35	35	35	35
Metalose	35	52.5	70	-----	-----	-----	35	35	35
H.P.M.C.K15CR	-----	-----	-----	35	52.5	70	8.75	17.5	35
Ethyl Cellulose	7	7	7	7	7	7	7	7	7
Pregelatinised Starch	27	27	27	27	27	27	27	27	27
Microcrystaline Cellulose	18	18	18	18	18	18	18	18	18
Lactose	44	26.5	9	44	26.5	9	35.25	26.5	9
P.V.P.K.30	7	7	7	7	7	7	7	7	7
I.P.A.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Aerosil	1	1	1	1	1	1	1	1	1
Talc	3	3	3	3	3	3	3	3	3
Mg.Stearate	3	3	3	3	3	3	3	3	3

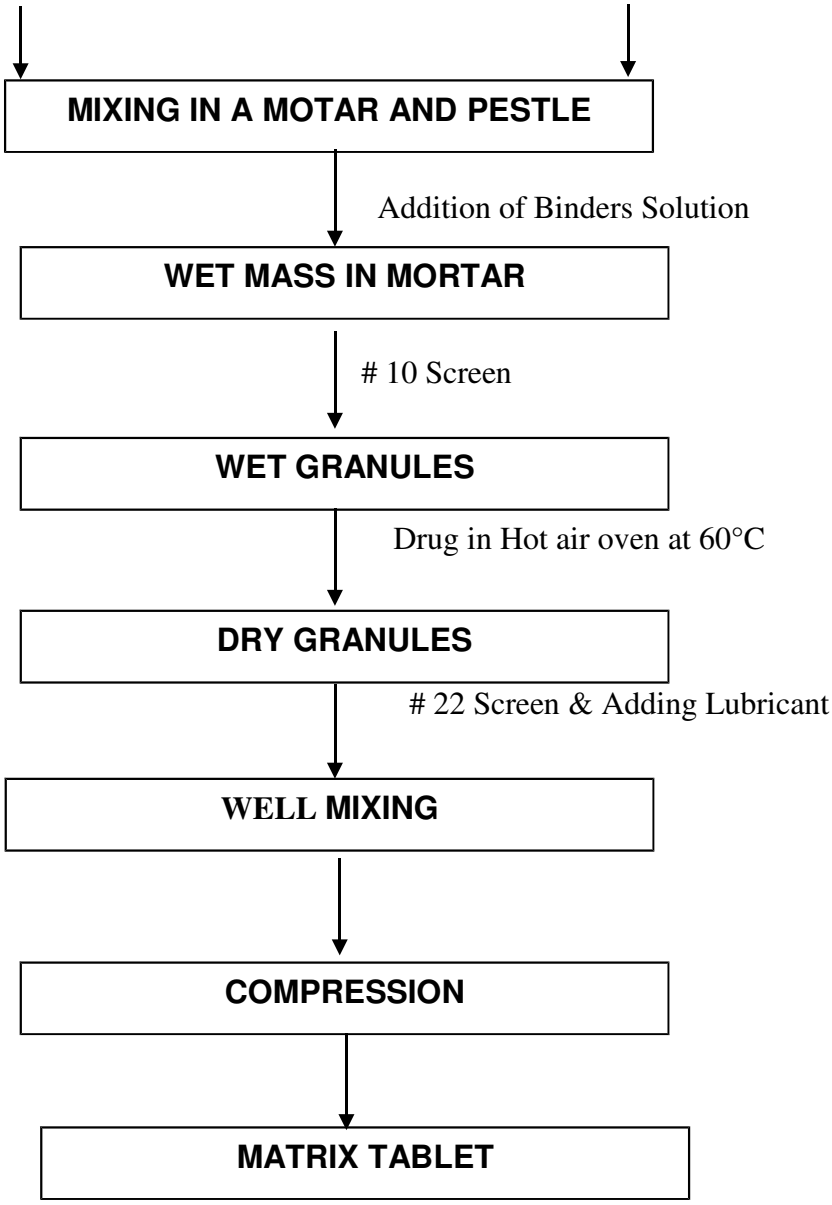

Figure No. 6:-Schematic representation of preparation of Matrix Tablet

6.8. COATING PROCEDURE

Weigh accurately H.P.M.C 6 CP and Ethyl Cellulose and mixed in half portion of I.P.A. Dissolve titaneous oxide, yellow iron oxide, talc in half portion of I.P.A. mix well half portion of metylene chloride was added in above solution.Dissolve PEG 6000 in half portion of methylene chloride and added to above solution and stirred well.

Table No. 6:-Coating Formula

S. No.	Ingradients	Quantity
1.	H.P.M.C. 6 cp	5 mg
2.	Etyl Cellulose	0.5 mg
3.	Polyethylene Glycol	1 mg
4.	Titanium Dioxide	1 mg
5.	Yellow Iron Oxide	0.5 mg
6.	Talcum	1 mg
7.	I.P.A.	0.15 ml
8	Methylene Chloride	0.2 ml

6.9 Evaluation of Tablets:

All the prepared Sustained release tablets were evaluated for following official and unofficial parameters.

- Weight Variation
- Thickness
- Hardness Test
- Friability Test
- Drug content
- Dissolution Study

6.9.1. Weight variation:

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the percentage shown in Table no.10 and none deviate by more than twice the percentage shown.

Table No.7:- Percentage deviation allowed under weight variation

Percentage deviation allowed under weight variation test.	
Average weight of tablet (X mg)	**Percentage deviation**
X < 80 mg	10
80 < X < 250 mg	7.5
X > 250 mg	5

6.9.2. Thickness

Twenty tablets were randomly selected from each batch and there thickness and diameter was measured by using digital vernier caliper.

6.9.3 Tablet Hardness

The crushing strength Kg/cm^2 of prepared tablets was determined for 10 tablets of each batch by using Monsanto tablet hardness tester. The average hardness and standard deviation was determined. The results are shown in Table No.10

.

6.9.4. Friability:

Method:

Twenty tablets were weighed and placed in the Electrolab friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dedusted and weighed again. The percentage friability was measured using the formula,

$$\% F = \{1-(W_t/W)\} \times 100$$

Where, % F = friability in percentage

W = Initial weight of tablet

W_t = weight of tablets after revolution

The results are shown in Table 10.

6.9.5 Assay Procedure: -

Standard preparation:

Transfer an accurately weighed quantity of about 40 mg of trimetazidine HCL to 200 ml volumetric flask. Dissolve and dilute to volume with 0.1 N HCL and makeup the volume.

Test preparation:

Crush 20 tablets and weigh accurately 40 mg of powder equivalent to the trimetazidine HCL into 200 ml volumetric flask. Dissolve and dilute to the volume with 0.1 N HCL and makeup the volume. Filter the test preparation through 0.45µ filter paper.

Measure the absorbance of standard and test at 269 nm and calculate trimetazidine HCL by the following equation:

$$\% \text{ ASSAY} = \frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \times \frac{\text{wt. of STD}}{200} \times \frac{200}{\text{test. Wt}} \times \frac{\text{avg. wt}}{\text{L.C.}} \times \text{potency}$$

The results are shown in Table No.10

6.9.6. In Vitro Dissolution Studies:

In Vitro dissolution study was carried out using USP I apparatus (basket apparatus) in 900 ml of phosphate buffer pH 6.8 for 8 hours. The temperature of the dissolution medium was kept at 37± 0.5°C and the basket was set at 100 rpm. 10 ml of sample solution was withdrawn at specified interval of time. The absorbance of the withdrawn samples was measured at λ_{max} 269 nm using UV visible spectrophotometer. The concentration was determined from the standard curve of Trimetazidine HCL prepared in phosphate buffer pH 6.8 at λ max 269 nm. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

6.9.7 Swelling Index[65]

The swelling index of tablets was determined in phosphate buffer pH 6.8 at room temperature. The swollen weight of the tablets was determined at predefined time intervals. The swelling index was calculated by the following equation:

$$\textbf{Swelling index WU} = \frac{(W_1 - W_0)}{W_0} \times 10$$

Where, W_t = Weight of tablet at time t.

W_0 = Initial weight of tablet

.

6.9.8 Modeling of Dissolution Profiles[66]

In vitro dissolution has been recognized as an important element in drug development under certain assessment of Bioequivalence. Several theories/kinetics models describe drug dissolution from immediate and modified release dosage forms. There are several models to represent the drug dissolution profiles where f_t is a function of't' (time) related to the amount of drug dissolved form the pharmaceutical dosage system (Costa and Lobo,2001).Whenever a new solid dosage form is developed or produced, the drug release/dissolution from solid pharmaceutical dosage form is necessary to ensure that the drug dissolution occurs in an appropriate manner.

The quantitative interpretation of the value obtained from the dissolution assay is facilitated by mathematical equation which translates the dissolution curve in function of some parameters related with the pharmaceutical dosage forms.

In the present study, data of the *in vitro* release were fitted to different equations and kinetic models to explain the release kinetics of Trimetazidine HCL from the matrix tablets. The kinetic models used were a Zero order equation, Higuchi release.

Drug release models:

To describe the kinetics of the drug release from the matrix tablet batches, mathematical models such as zero-order, first order, Higuchi, Hixon-crowell models were used. The criterion for selecting the most appropriate model was chosen on the basis of the goodness-or fit test.

The zero-order kinetic describes the systems in which the drug release rate is independent of its concentration. The first order kinetic describes the systems in which the drug release rate is concentration dependent. Higuchi described the release of drug from an insoluble matrix as square root of time dependent process.

In case of the Higuchi square root model gives the drug release from a planer surface of an insoluble heterogeneous matrix by diffusion through the intragranular openings created by porosity of the matrix tablet.

6.10 Stability Studies[67]

Selected formulations were subjected to stability studies as per I.C.H. Guidelines.

Following conditions were used for stability studies

- 30°C/65 % RH analyzed till a period of 30 days
- 40°C/75 % RH analyzed till a period of 30 days

Following parameters were check for stability studies

Hardness, friability, drug content and in vitro release.

RESULTS AND DISCUSSION

7.1 IDENTIFICATION OF DRUG:-

7.1.1 FTIR Spectra:

IR spectra of drug in KBr pellets at moderate scanning speed between 4000-400 cm^{-1} was carried out using FTIR (Jasco FTIR 6100 type A). The peak values (Wave number) and the possibility of functional group shown in spectra which compare with standard value.

The comparison of these results with trimetazidine HCL chemical structure shows that the sample was pure Trimetazidine HCL. Figure No.7.

7.1.2 UV absorption maxima of Trimetazidine HCL:

UV scanning was done for 10 mcg/ml drug solution from 200-400 nm in 0.1 N HCL as a blank using double beams UV/VIS spectrophotometer. The wavelength maximum was found to be at 269 nm (Figure No. 11).

7.2 Drug Excipients Compatibility study:

Compatibility of the drug with recipients was determined by FT-IR spectral analysis, this study was carried out to detect any changes on chemical constitution of the drug after combined it with the excipients.

The samples were taken for FT-IR study. (Figure No. - 8, 9, 10).

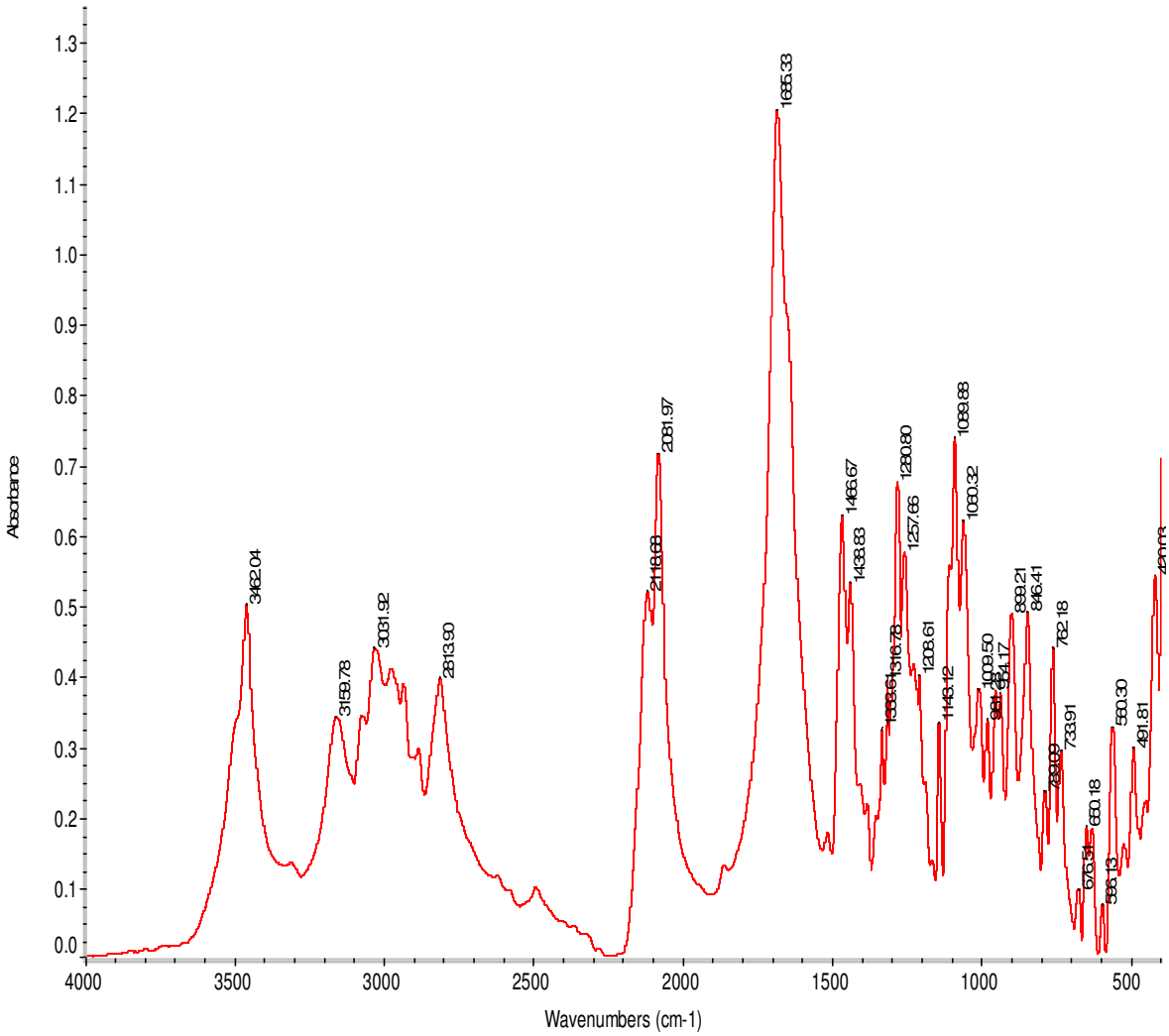

Figure No. 7:- IR Spectrum of Pure Drug (Trimetazidine HCL)

7.2.1 Drug Excipients Compatibility study:

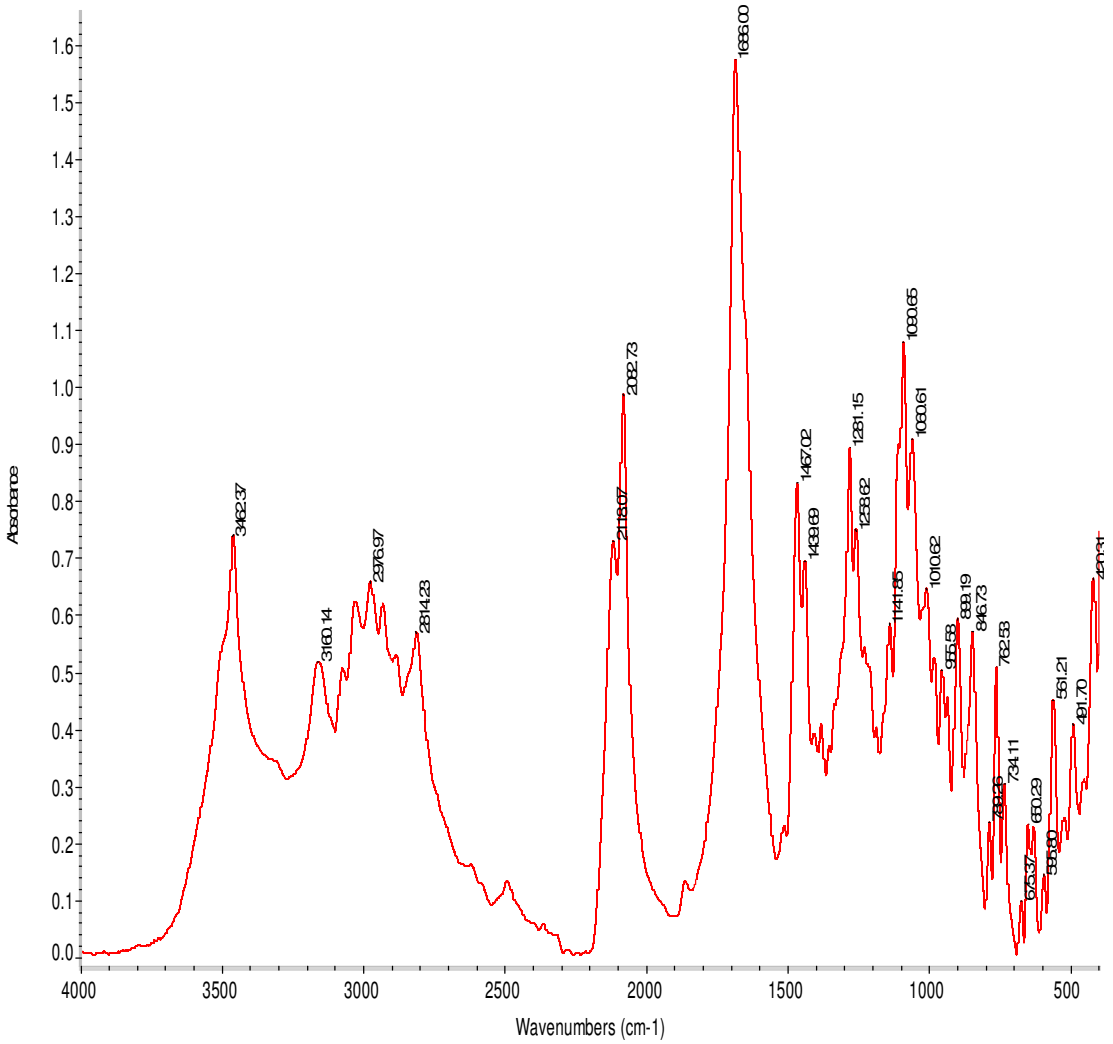

Figure No. 8:- IR Spectrum of drug + HPMC K15 CR

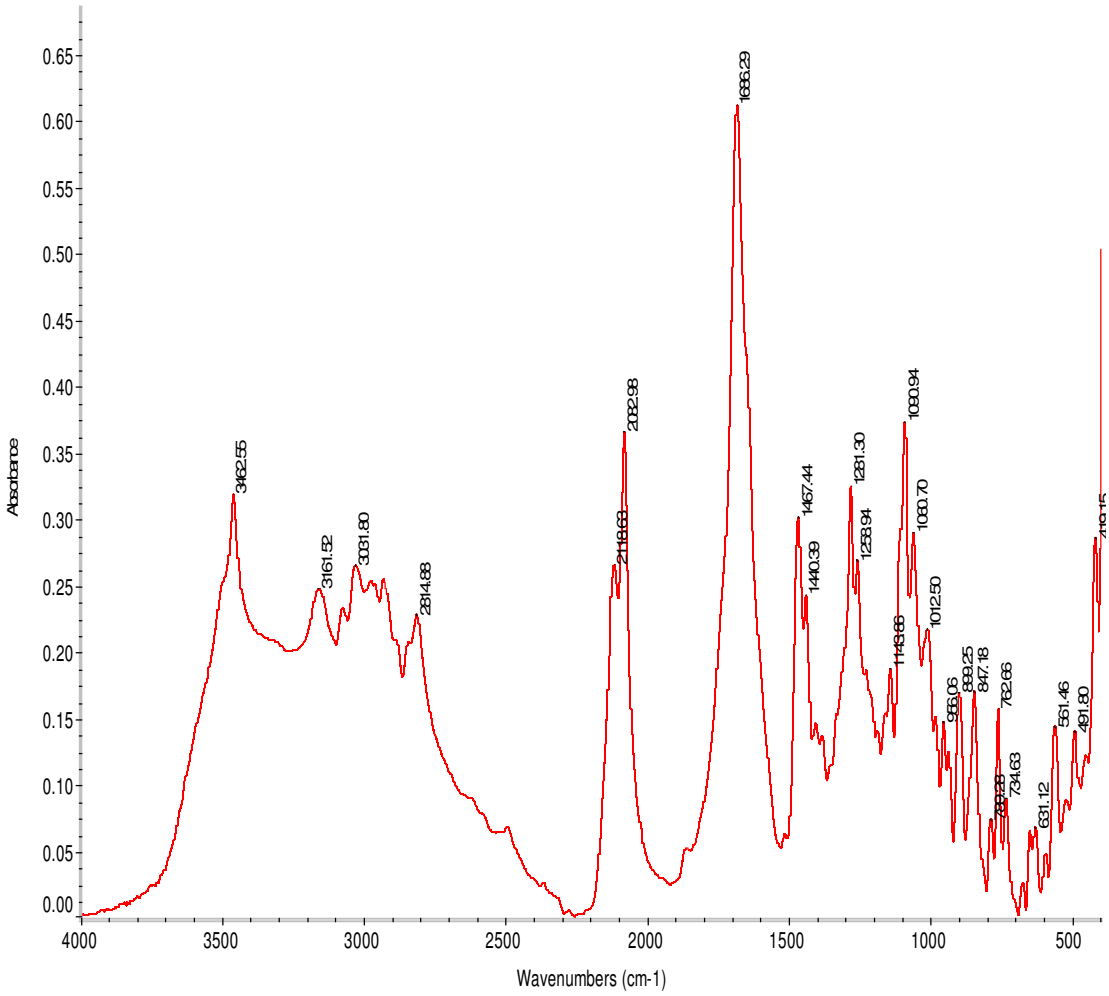

Figure No. 9:- IR Spectrum of Drug + Metalose

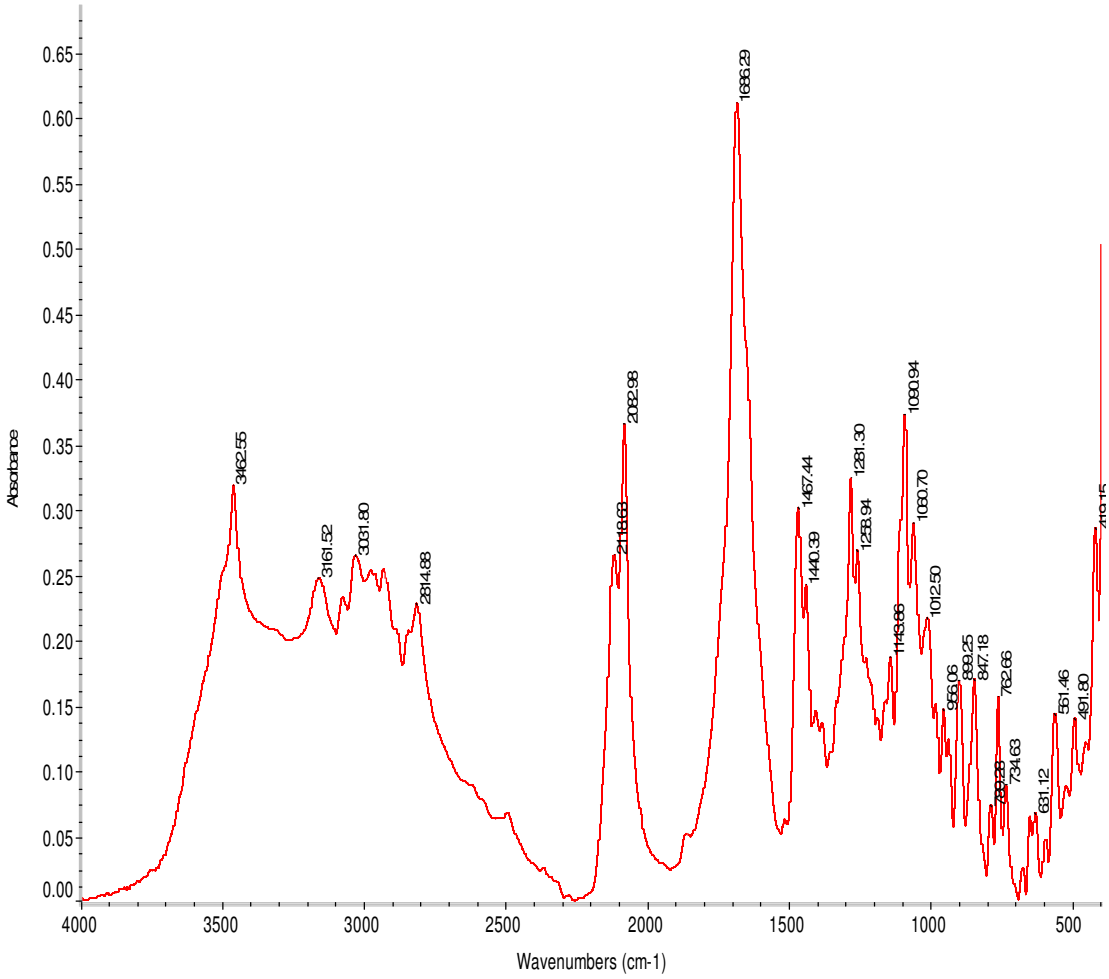

Figure No.10:-IR Spectrum of Drug + Ethyl cellulose

IR spectra studies revealed that the drug and polymers used were compatible.

7.3 Determination of λ max:

Figure No.11:-Absorbance Maxima of Trimetazidine HCL

7.4 Calibration Curve of Trimetazidine HCL

Table No. 7:- Calibration curve of Trimetazidine HCL

Concentrarion	Absorbance at 269nm
0	0
3	0.049
6	0.105
9	0.162
12	0.217
15	0.266
18	0.321
21	0.386
24	0.433
27	0.495
30	0.587

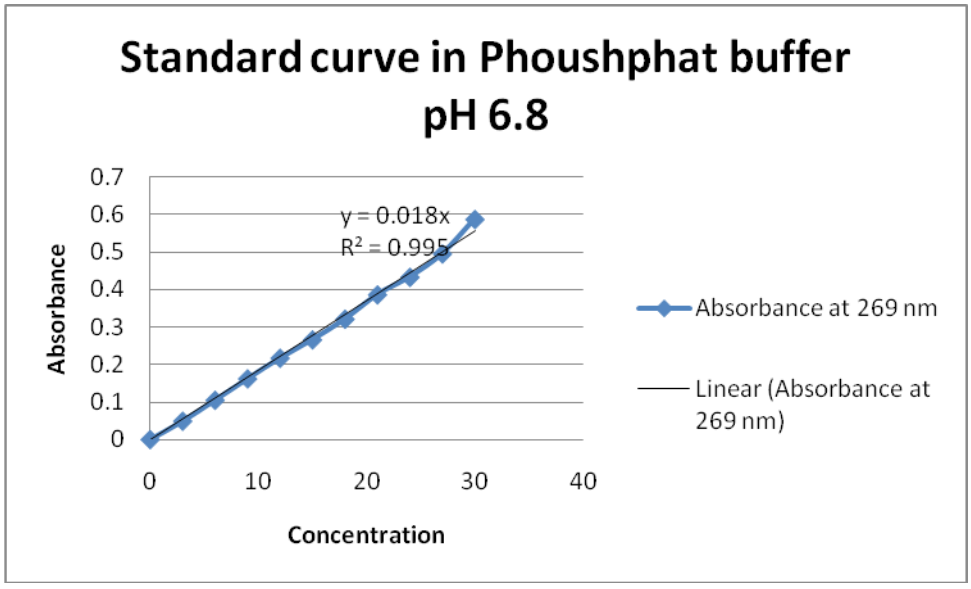

Figure No. 12:- Calibration Curve of Trimetazidine HCL

7.5 Evaluation of Powders:-

7.5.1 Preformulation Studies:-

Table No.8:- Preformulation studies of pure drug and polymers

Parameter	Results			
	Trimetazidine HCL	**HPMC-K-15 CR**	**Metalose**	**Etyl Cellulose**
Angle of Repose	24	22	19	26
Bulk Density (gm/cm^3)	0.46	0.31	0.35	0.60
Tapped Density (gm/cm^3)	0.72	0.52	0.59	0.77
Compressibility Index	36.11	40.34	40.67	22.07
Hauser's Ratio	1.56	1.60	1.68	1.28

Table No. 9:- Preformulation studies of blend

BATCH NO.	BULK DENSITY (g/ml)	TAPPED DENSITY (g/ml)	COMPRSIBILITY (%)	HOUSNER RATIO	ANGLE OF REPOSE (°)
F1	0.314	0.389	19.2	1.237624	25^0
F2	0.368	0.426	13.6	1.157407	18^0
F3	0.399	0.476	16.2	1.193317	20^0
F4	0.354	0.416	17.51	0.86	$29^011'$
F5	0.399	0.476	16.2	1.193317	$20^o12'$
F6	0.421	0.512	17.7	1.215067	23^0
F7	0.458	0.534	14.3	1.166861	20^0
F8	0.316	0.409	29.43	0.77	$31^016'$
F9	0.366	0.457	24.86	0.80	24^0

Preformulation study was done initially and results directed for the further course of formulation. Based on Preformulation studies different batches of Trimetazidine HCL (F1 to F9) were prepared using selected excipients.

Powders were evaluated for tests Angle of repose, Bulk density, tapped density, compressibility index, Hausner ratio before being punched as tablets.

7.5.2 Physico-Chemical Evaluation of Matrix Tablets:

The results of the thickness, Hardness, weight variation, drug content, friability, disintegration time of tablet are shown in Table No.10.

Table No. 10:- Results of Thickness, weight variation, Hardness, Friability and Drug content

BATCH NO.	WEIGHT VARIATION	FRIABILITY (%)	HARDNESS (kg/cm^2)	THICKNESS (mm)	DRUG CONTENT (%)
F1	±4.0	0.12	4.5	3.9	96.20
F2	±2.0	0.19	5	4	97.26
F3	±3.0	0.39	5	4.1	98.93
F4	±2.55	0.14	5	4	97
F5	±2.0	0.24	5	3.9	99.89
F6	±3.44	0.11	5.5	3.8	98.53
F7	±2.0	0.43	4	4.1	97.11
F8	±5.66	0.16	5	3.9	97
F9	±5.22	0.18	5.5	3.8	96.00

7.5.3 In Vitro Dissolution Studies

Table No.11 shows the data for in vitro release of Trimetazidine HCL from matrix tablet of batches F1, F2, F3, F4, F5, F6, F7, F8 and F9 respectively.

As follows the dissolution profiles shows the comparative release profile of Trimetazidine HCL with different concentration of different polymer from batches F1, F2, F3, F4, F5, F6, F7, F8, F9 of matrix tablet.

Table No. 11:- Cumulative % Release of Drug of various Formulations

Time(Hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	40.5	41.1	42.31	38.25	45.04	36.83	33.78	37.47	34.61
2	54.44	59.07	58.14	48.75	54.14	51.01	45.73	55.06	50.36
4	80.51	84.25	81.38	81.18	78.1	73.38	67.16	77.81	68.95
6	88.23	90.08	89.99	89.99	85.31	84.43	72.93	85.52	72.98
8	91.19	92.86	92.95	92.95	86.84	89.96	85.02	87.75	80.77

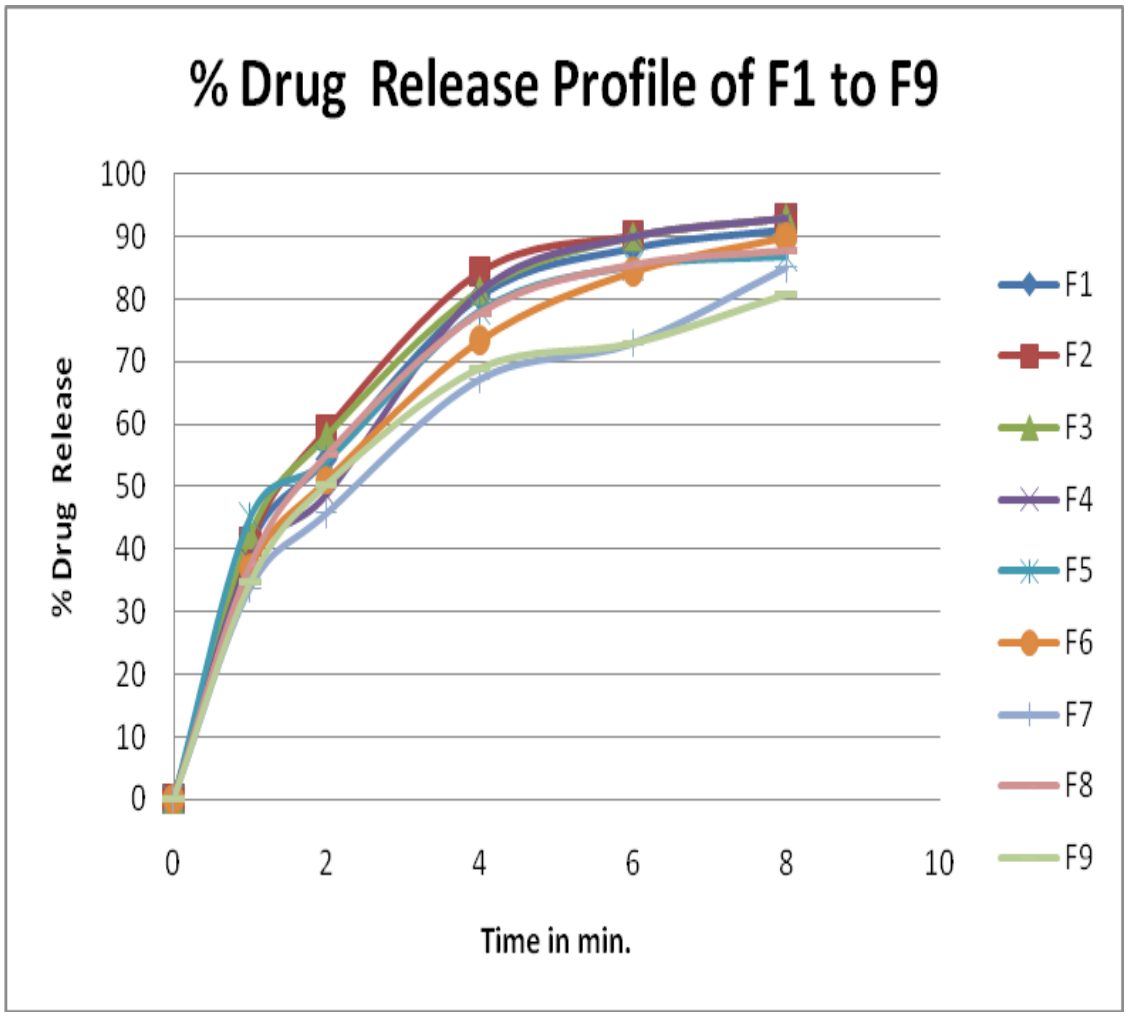

Figure No.13:- Graph of the Cum. % drug release versus Time (hrs)

7.5.4. % Swelling Index of Tablets of Batch F1 toF9

Batch	TIME (HRS)						
	0	1	2	3	4	5	6
F1	0	32.23	41.38	54.32	63.78	74.12	81.2
F2	0	49.25	61.54	72.90	82.37	92.54	100.22
F3	0	29.09	39.45	51.32	61.12	71.97	80.35
F4	0	39.21	51.92	63.76	72.52	84.2	96.56
F5	0	45.65	53.35	64.32	75.45	80.09	94.58
F6	0	56.73	66.76	77.72	82.26	94.60	101.25
F7	0	39.06	47.96	55.32	65.34	76.09	87.11
F8	0	25.87	36.54	47.86	57.98	69.96	72.44
F9	0	26.76	40.98	49.54	59.06	69.78	75.99

Table No.12:- % Swelling Index of Tablets of Batch F1 toF9

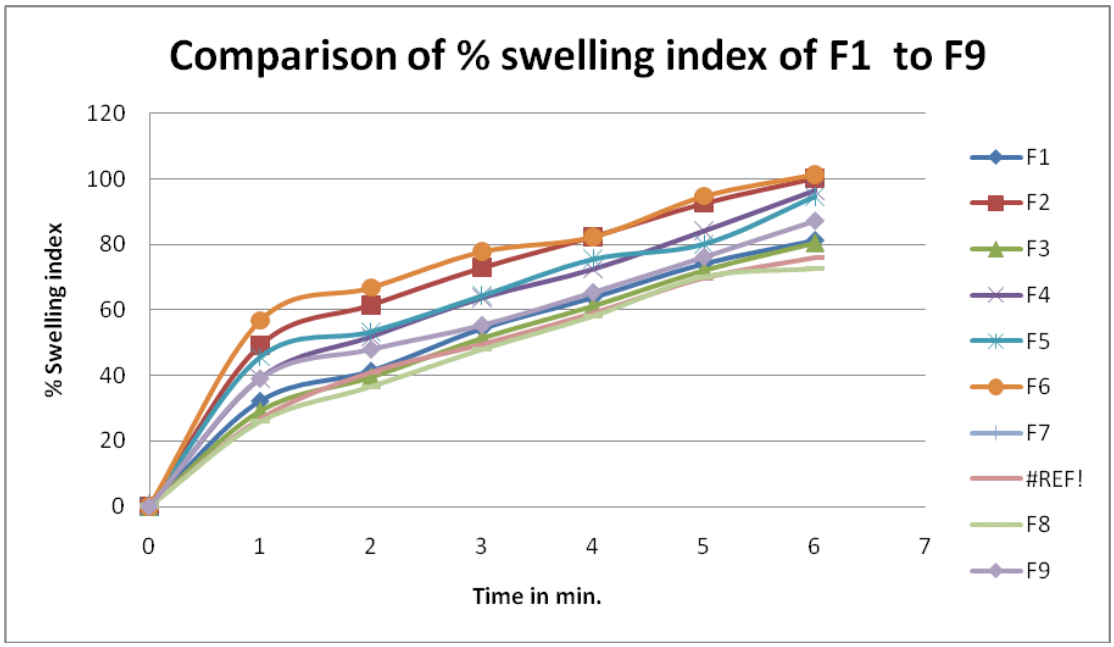

Figure No. 14:- Comparison of % swelling index of various formulations

7.5.5 Kinetic assessment of Extended release Matrix tablet containing Trimetazidine HCL-

Huguchi Modeling -

Table No. 13:- Huguchi Modeling

BATCHES	R^2 VALUE (ZERO ORDER)	R^2 VALUE (HUGUCHI)
F1	0.809	0.971
F2	0.787	0.961
F3	o.798	0.969
F4	0.802	0.975
F5	0.768	0.955
F6	0.851	0.988
F7	0.865	0.991
F8	0.802	0.968
F9	0.807	0.973

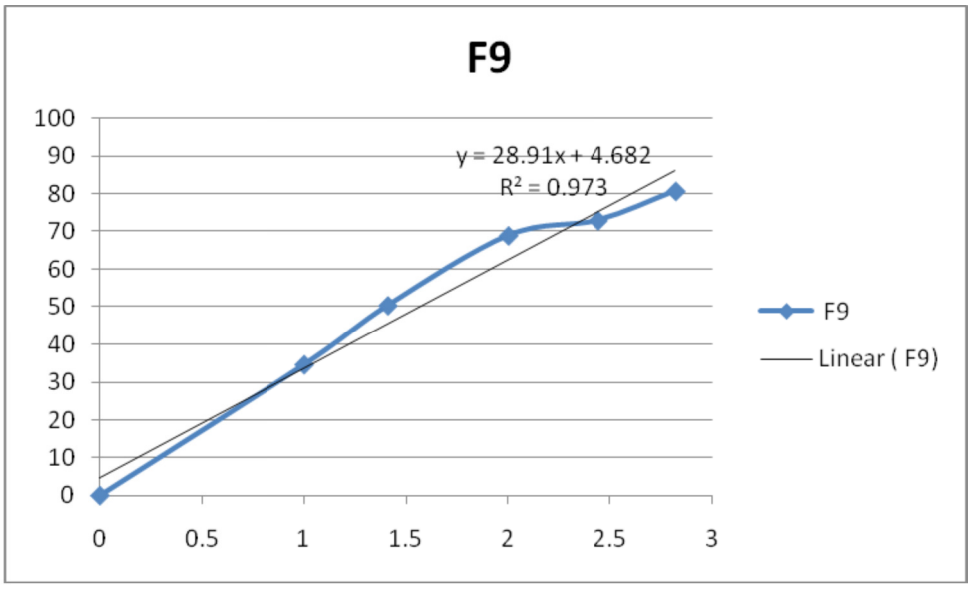

Figure No. 15:- Huguchi Modeling

Figure No. 16:- Zero order Modeling

7.6 Stability Study of Optimized Formulation: -

As per I.C.H. Guidelines

Table No. 14: Stability studies of formulation F-9 stored at 30°C/65 % RH

Time (hr)	Cumulative % Drug Release	
	Initial	After 30 Days
0	0	0
1	34.61	34.01
2	50.36	50.98
4	68.95	67.33
6	72.98	71.61
8	80.77	80.11
Hardness	5.5	5.5
Friability	0.18	0.17
Drug content	96	95.92

Table No-15:- Stability studies of F-9 stored formulation at 40°C/75 % RH

Time (hr)	Cumulative % Drug Release	
	Initial	After 30 Days
0	0	0
1	34.61	33.53
2	50.36	50.12
4	68.95	66.65
6	72.98	72.53
8	80.77	79.78
Hardness	5.5	5.5
Friability	0.18	0.18
Drug content	96	94.99

SUMMARY AND CONCLUSION

Oral route of drug administration is oldest and safest mode of drug administration. It posses several advantages. It provides accurate dosing without assistantship of administration. In conventional oral drug delivery system, there is little or no control over release of drug, and effective concentration at the target site can be achieved by administration of grossly excessive dosage form. Sustained release technology is relatively new field and as a consequence, research in the field has been extremely fertile and has produced many discoveries. With many drugs, the basic goal is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage form is an important element to accomplish this goal.

Trimetazidine HCL is Vasodilator with half life of 6 hours and requires multiple daily doses to maintain adequate plasma concentrations. So it is selected to prepare an extended release Matrix tablet. The objective of this present study is to develop an extended release Matrix tablet of Trimetazidine HCL which releases the drug in an extended manner over a period of 8 hours, by using different polymers and study on polymer concentration effect on release pattern.

The present study was undertaken with an aim to formulate develop and evaluate Trimetazidine HCL extended release matrix tablets using different polymers as release retarding agent.

Preformulation study was done initially and results directed for the further course of formulation. Based on Preformulation studies different batches of Trimetazidine HCL were prepared using selected excipients. Powders were evaluated for tests Angle of repose, Bulk density, tapped density, compressibility index, and Hausner ratio before being punched as tablets.

IR spectra studies revealed that the drug and polymers used were compatible.

Various formulations of sustained release matrix tablets of Trimetazidine HCL were developed using various polymers viz, HPMC K-15CR, Hypermellose, Ethyl Cellulose in different proportions and combinations by Wet Granulation technique. The tablets were evaluated for physical characterization, *in vitro* swelling behavior, *in vitro* release study and stability studies.

Observations of all formulations for physical characterization had shown that, all of them comply with the specifications of official pharmacopoeias and/or standard references.

Results of *in vitro* release profile indicated that formulation F9 was the most promising formulation as the extent of drug release from this formulation was high as compared to other formulations. Results of in-vitro swelling study indicate that the formulation F9 was having considerable swelling index.

Stability study was conducted on tablets of Batch F9 stored at 30^0C (Room Temperature) and 40^0C for one month. Tablets were evaluated for hardness, friability, in-vitro release profile and drug content. After one month no significant changes were observed in any of the studied parameters during the study period, thus it could be concluded that formulation was stable. It was concluded that the tablets of batch F9 had considerable swelling behaviors and *in vitro* drug release. Percentage drug release in 8 hr is 80.77. It was observed that tablets of batch F9 followed the Huguchi release profiles.

From the above results and discussion it is concluded that formulation of Extended release matrix tablet of Trimetazidine HCL containing HPMC K-15 (19.44%) and Hypermellose (19.44%), Ethyl cellulose (19.44%) batch F9 can be taken as an ideal or optimized formulation Extended release matrix tablet for 8 hour release as it fulfills the requirements for extended release matrix tablet.

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